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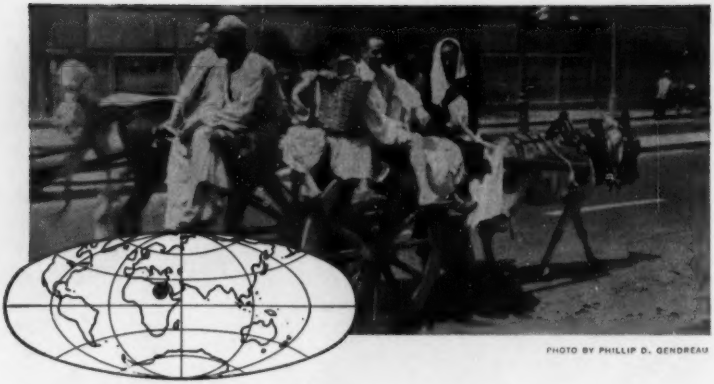

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THE American Journal OF Gastroenterology

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contents:

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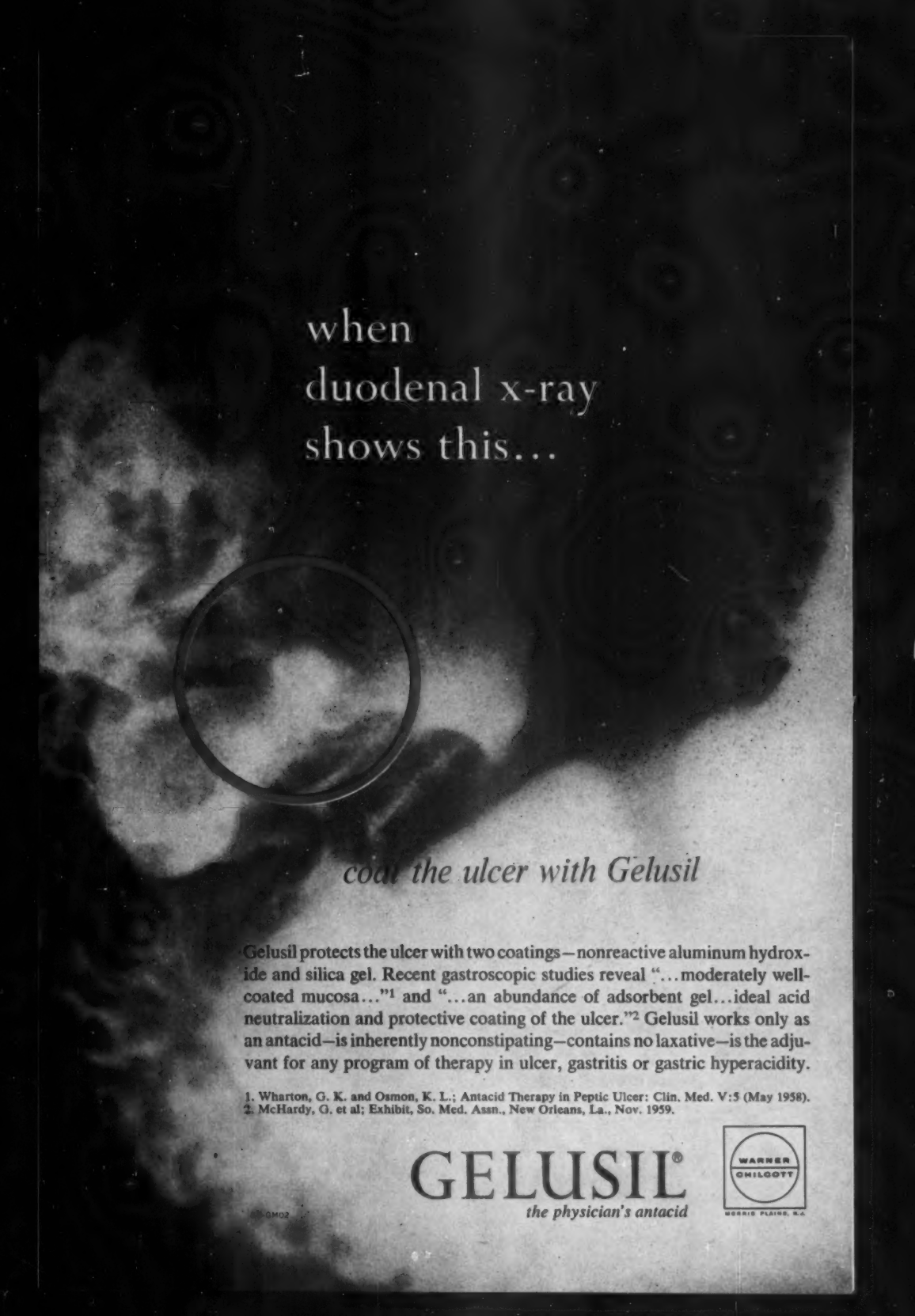

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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V:5 (May 1958).
2. McHardy, G. et al; Exhibit, So. Med. Assn., New Orleans, La., Nov. 1959.

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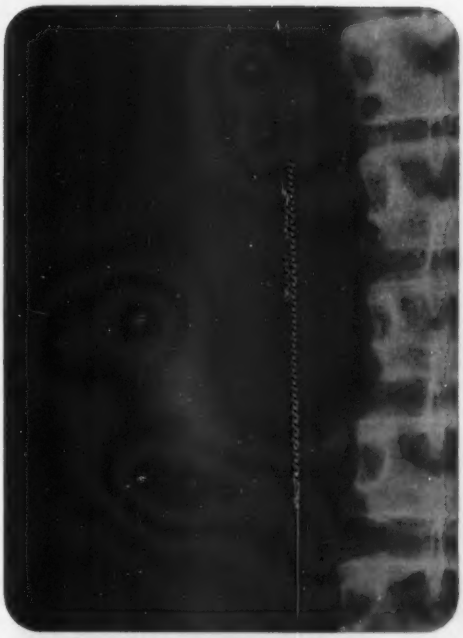

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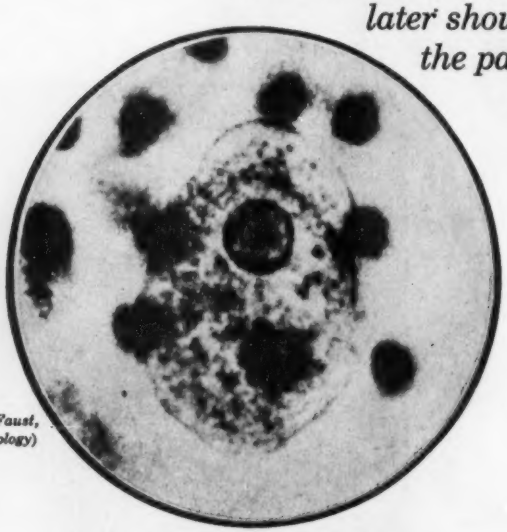

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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). (To be published in Am. J. Gastroenterol., October, 1960.)

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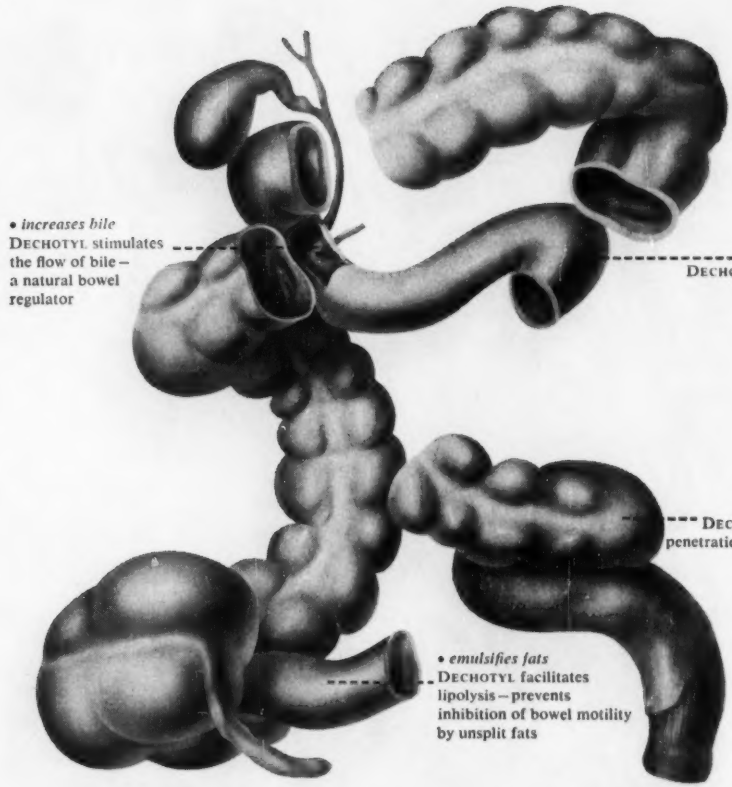

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VOLUME 34 OCTOBER, 1960 NUMBER 4

PANEL DISCUSSION ON PANCREATIC DISEASE*

DONALD E. ROSS, M.D., F.A.C.S., F.A.C.G., *Moderator*†

JACK M. FARRIS, A.B., B.Sc., M.D.‡

Los Angeles, Calif.

JULIAN H. FRIEDEN, M.D.¶

Beverly Hills, Calif.

EDWARD M. GREANEY, JR., B.S., M.D.§

North Hollywood, Calif.

and

PAUL H. GUTH, B.S., M.D.**

Orange, Calif.

Dr. Donald E. Ross:—Good morning, my distinguished colleagues. By way of introduction I may say that we are dealing this morning with questions concerning the pancreas. It is such a monumental subject that we felt it imperative to restrict the subject to pancreatitis. We have invited a group of distinguished doctors who will discuss this problem, and I am sure we are going to hear a lot of important things.

Introducing, first to my left, Dr. Edward Michael Greaney, a very fine surgeon in this city and an Instructor in the Department of Surgery at the University of Southern California. Seated next to him is Dr. Jack Farris who really needs very little introduction. He has had marvelous training and has tremendous experience in pancreatic difficulties.

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*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Los Angeles, Calif., 24, 25, 26 September 1959.

†Chief Surgeon, Ross-Loos, Medical Group.

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The next gentleman is Dr. Paul Guth, who incidentally is the only medical man on the panel this morning. Dr. Guth is Director of Gastroenterology at the Orange County Hospital. Being the only medical man on the panel, I am afraid we are going to work him pretty hard.

At the end of the table is Dr. Julian Frieden, Instructor in Surgery at University of Southern California. A very distinguished surgeon. Dr. Frieden has written many articles on the subject of pancreatitis and has performed a lot of research work on the subject.

As a preliminary to the discussion, and while you are getting your thinking caps on about questions, each doctor on the panel is going to give a short introductory address on some phase of pancreatitis.

First I would like to ask Dr. Farris to introduce the subject, because he wants to talk particularly on the etiological principles in the treatment of pancreatitis and I think this would be a very good introduction. Dr. Farris.

Dr. Jack M. Farris:—I assume that being on a panel allows one to talk while sitting down, so if you will excuse me I won't stand at the rostrum.

As our Moderator has implied, the proper approach to either medical or surgical treatment of a given disease is founded upon some knowledge of the physiological principles involved. And, as in so many realms of surgical and medical endeavor, I think progress has been a rather direct result of contributions from the basic sciences, and certainly the pancreas is no exception.

As you know, the pancreas is under endocrine, hormone, enzymatic and nervous control, and proper understanding of these features allows us to properly manage cases of acute and chronic pancreatitis. May I have the first slide, please?

(Slide) This slide is a diagrammatic illustration of the biliary and pancreatic duct systems. It is almost impossible, I think, to discuss the pancreatic duct system without implicating the biliary duct system. This is a very busy part of the gastrointestinal tract. Enormously important is this centimeter or two of intestinal continuity. It is probably more critical than any other area in the gastrointestinal tract. Anywhere from two or three liters of fluid are extruded between these openings in a 24-hour period, about half of it coming from the liver and bile ducts and half of it coming from the duct of Wirsung and the duct of Santorini, which usually opens independently into the mucosa.

The juices, as you know, contain three important enzymes: trypsin, amylase, and lipase. It is interesting that if the pancreatic juice is collected before it comes in contact with the duodenal mucosa, the digestive potential is lost. If, however, the pancreatic juice is allowed to come in contact with the mucosa even momentarily, it now has a potent or powerful proteolytic activity. This

explains, I am sure, why pancreatic fistulas in the human being do not digest the abdominal wall.

Amylase is extremely powerful. When the duct is obstructed we get high levels of amylase in both the urine and blood.

Lipase activity is also of significance, splitting fat into fatty acids and glycerine, and fatty acids, combine with alkalis such as calcium to form soaps.

These three enzymes, when blocked, are excluded from the gastrointestinal tract, as in chronic pancreatitis, and produce rather profound digestive disorders, and can be detected by proper analysis of the stools.

So much for the enzymatic aspects of the pancreatic duct system.

It was shown in 1902 that a mixture of duodenal mucosa and hydrochloric acid, when given intravenously to an animal, will produce a potent pancreatic stimulation. Hydrochloric acid alone does not produce this phenomenon. It was therefore ascertained that there was a *hormone* in the mucosa which had to be activated by hydrochloric acid, and this *hormone*, as you know, is called *secretin*. This bit of information forms the background for many of our surgical attacks upon both the vagus apparatus and also upon the stomach itself in the surgical treatment of chronic relapsing pancreatitis.

Now about the nervous control. It has been shown that if you divide the vagus, for example, in the neck of an animal, and wait two days and stimulate the distal portion, there is an outflowing of pancreatic juice which is somewhat less than that produced by secretin. Whereas the material collected for secretin is of high volume, it is low in enzymes, while the one from the vagus stimulation is low in volume and very rich in enzymes, and again forms the physiologic background for attacks upon the vagus nerves and also for the use of many drugs for the treatment of acute pancreatitis.

The internal secretion (insulin) is under the control of endocrines, as you know. The anterior lobe of the pituitary produces an andrenotropic hormone, the absence of which may be responsible for diabetes, and it is interesting that diabetes following pancreatectomy may be ameliorated by adrenalectomy, particularly if animals are sustained with cortisone.

(Slide) These are personal slides of cases where the duct system has been injected with radioopaque material, usually with a T-tube, or in this instance in a gallbladder where a cholecystostomy has been done. Here you see the reflux of the radioopaque material into the main pancreatic duct. It shows quite well in these two.

This lends support to the so-called common channel theory; that is, that pancreatic juices and bile juices empty into a common opening, and under certain circumstances, particularly after a large meal, where there is increased

biliary pressure, there may be a reflux of bile and other digestive products into the pancreatic duct. Workers in this field feel that this phenomenon is responsible for the episode of acute pancreatitis.

Without boring you with the details, approximately two-thirds of all human beings have an ampulla into which both the pancreatic and common duct open. One-third of all human beings examined have shown a separate opening of these two. In general only about 50 per cent of all human beings are capable of reproducing the so-called common duct channel theory (injection studies in cadavers).

With these preliminary remarks I will say again that I think contributions in this field probably will continue to come from critical observations, not only in clinical work but also in the basic sciences.

Dr. Ross:—The next speaker will be Dr. Paul Guth, who is our medical man on the panel, and he will give us a few of the highlights of the laboratory diagnosis of pancreatitis.

Dr. Paul H. Guth:—It is extremely difficult, if not impossible, to make an unequivocal diagnosis of acute pancreatitis by bedside examination alone. Fortunately, certain laboratory determinations are of pathognomonic value in the early diagnosis of acute pancreatitis. The serum amylase determination is the one most important test, and an elevated serum amylase level has been termed the *sine qua non* of a valid diagnosis of acute pancreatitis. The serum amylase concentration is elevated early in the course of acute pancreatitis, and falls to normal levels in two to three days. There is no constant relationship between the severity of the disease and the height of the serum amylase concentration. Serum amylase elevations occur in acute abdominal conditions other than acute pancreatitis, e.g., cholecystitis, peptic ulcer and peritonitis, thus placing serious limitations on its significance. It is unusual, however, for the serum amylase to rise above 500 Somogyi units in abdominal conditions other than primary disease of the pancreas.

One aid in such problem cases is a diagnostic tap of the peritoneum. The presence of clear yellow to brown fluid with an elevated amylase concentration yields a rapid differential from the bile of a perforated gallbladder, the cloudy fluid of perforated peptic ulcer, or the pus and *E. coli* organisms found with a ruptured diverticulum or appendix.

A diagnostic problem also arises in the case of acute pancreatitis that has partially subsided or in the atypical case with normal or equivocal serum amylase levels. Urine amylase determinations may be of value in such instances. Budd and his co-workers[1] have recently evaluated and reported on urine amylase, using the Somogyi iodimetric technic for measurement of amylase. They found the 24-hour urine determinations were subject to less variation than a six-hour determinations. The average 24-hour urine amylase output was 3,000

units, with a normal range of 800 to 6,000 units. The urine amylase values were elevated early in acute pancreatitis and remained elevated for longer periods than the serum amylase concentrations, for as long as one to two weeks in some instances. Elevated urine amylase levels were also found in some cases of chronic pancreatitis presenting with low serum amylase concentrations.

Serum lipase determinations are also of importance diagnostically. It has been reported that elevation of serum lipase persists after amylase levels have returned to normal[2]. In our experience, however, serum lipase concentrations parallel the rise and fall of serum amylase concentrations. The usefulness of the standard Cherry and Crandall method is impaired by the fact that the test requires a 24-hour incubation period. Several recently described modifications employing shorter incubation periods[3] and the rapid phototurbidometric technic we have described[4] may prove to be of value for this reason.

Since blood contains trypsin inhibitors, serum trypsin cannot be easily measured. Nardi[5], on the basis of experimental work by Bergmann indicating a relative specificity of trypsin for certain peptide linkages, has employed alpha benzoyl-l-arginine amide hydrochloride as a substrate for measuring what he considers to be true serum trypsin levels. He reported significant elevations in most cases of acute pancreatitis and in carcinoma of the pancreas. Brown[6] has also studied the proteolytic activity of serum, using a slightly different peptide substrate. Inasmuch as there is evidence that the proteolytic activity of serum is not due to pancreatic trypsin, he refers to his method as measuring arginine exopeptidase activity. He found elevated exopeptidase activity in acute pancreatitis and in carcinoma of the pancreas. Rutenburg, Goldbarg and Pineda[7] have used still another peptide substrate to measure what they term serum leucine aminopeptidase activity. Increased peptidase activity was noted in acute pancreatitis and in carcinoma of the pancreas. After by-pass surgery to relieve the common duct obstruction in the patients with carcinoma of the pancreas, serum peptidase activity decreased progressively. They, therefore, believe that biliary tract obstruction, rather than pancreatic disease *per se*, is responsible for the increased leucine aminopeptidase levels. Elevated serum and urine leucine aminopeptidase activity was noted in all of the twenty cases of carcinoma of the pancreas. Regardless of the cause of the elevations in carcinoma of the pancreas, these results were so striking that one must concur with the authors' conclusion that normal urine and serum leucine aminopeptidase levels militate against the diagnosis of carcinoma of the pancreas.

In reviewing the results of these three methods for peptidase determination, Nardi's "trypsin" method, Brown's arginine exopeptidase method and Rutenburg and Goldbarg's leucine aminopeptidase method, one is struck by the similarity of the results in acute pancreatitis and carcinoma of the pancreas. Enzyme specificity often is relative and enzymes that attack a specific substrate readily will often also act on related substrates, although at a slower rate. Thus it is

possible that these three enzyme technics are all measuring the same enzyme or group of enzymes. Further studies are needed to clarify this point.

The last group of tests I would like to discuss are those measuring pancreatic insufficiency.

Careful investigation of the stool for undigested food may give the first suggestion of pancreatic insufficiency. On gross examination the feces are bulky and light in color, often almost white. On microscopic examination, large numbers of undigested muscle fibers as well as large quantities of fat in the form of neutral fat, fatty acids and soaps may be seen. Sudan III will stain the neutral fat droplets red and the fatty acid flakes orange, but the soaps will remain unstained. If a drop of 30 per cent acetic acid is added and brought to the boiling point over a flame, fatty acids are liberated. These will then take up Sudan III and stain orange. This step should not be omitted in the microscopic examination of feces, as large quantities of fat may otherwise be overlooked if they consist mainly of soaps. Chemical study of the feces is still one of the best methods available for the detection of malabsorption. The patient should be on a standard test diet containing a known amount of fat and protein, and the stools should be collected over a 72-hour period. On a diet containing 100 gm. of fat and 19 gm. of nitrogen, the normal person will excrete less than 7 gm. of fat and less than 2.5 gm. of nitrogen per 24 hours.

The secretin test is another important and physiologic test of pancreatic function. In this test a double-lumen tube is introduced, with one tube remaining in the stomach and the other in the duodenum. A fasting sample of the duodenal contents is obtained, and then pancreatic flow is stimulated by the administration of intravenous secretin. During the ensuing 60 minutes the duodenal content is collected and then analyzed for volume, bicarbonate concentration and amylase content. If carefully conducted, the secretin test will provide evidence of disturbance of pancreatic function in a considerable portion of cases before the sequela of calcification, diabetes and steatorrhea have appeared. The test will not distinguish the disturbed pancreatic function due to chronic pancreatitis from that due to carcinoma of the pancreas. Unfortunately the test is somewhat difficult to perform, requiring a rather high degree of technical skill, and is time-consuming. In addition, equivocal results are not infrequent early in the course of pancreatitis.

The intestinal absorption of I^{131}-labeled triolein and oleic acid has recently come into extensive use for the diagnosis of pancreatic exocrine insufficiency and for the differentiation of malabsorption due to pancreatic disease from that due to intestinal disease. The neutral fat triolein cannot be absorbed directly. It must first be hydrolyzed by pancreatic lipase into glycerol and oleic acid. These two fractions are then absorbed through the intestinal mucosa. By labeling the oleic acid portion of the triolein with I^{131}, the radioactivity of the blood and/or the stool following the ingestion of the triolein can be used as a measure

of the degree of digestion and absorption of the fat. In pancreatic exocrine insufficiency there is less digestion of the fat, and hence the radioactivity of the blood will be decreased while that of the stool will increase. In malabsorption states due to intestinal disease, e.g., sprue, although sufficient pancreatic lipase is present to digest the fat, the intestinal mucosa is unable to absorb normal amounts of oleic acid. Thus the I^{131}-triolein test will yield similar results in both pancreatic and intestinal malabsorption states. The I^{131}-labeled oleic acid test may then be used to differentiate these two disease groups. The oleic acid requires no further digestion by pancreatic enzymes and hence the patient with pancreatic insufficiency will absorb normal amounts of oleic acid with resultant normal levels of radioactivity in the blood and stool. The patient with intestinal malabsorption, however, is unable to absorb the oleic acid, with resultant decreased levels of blood radioactivity and increased levels of fecal radioactivity.

Dr. Ross:—Thank you, Dr. Guth.

Next we will hear from Dr. Frieden. I believe his remarks will have to do with the surgical therapy of acute pancreatitis.

Dr. Julian H. Frieden:—The treatment of choice for acute pancreatitis is generally considered to be medical. On occasions surgical intervention might be indicated during the acute phase of this disease. The mortality rates following the acute attack have been variously reported and are dependent upon the extent and type of the underlying pathologic process. Raker and Bartlett[14] found 16 patients or 12 per cent died during the acute attack in their series of 134 patients with acute pancreatitis. Mackenzie[11] reported a 9.3 per cent mortality rate in 54 cases treated medically during the acute phase. Siler[16] reported an over all mortality rate of 14.4 per cent in a group of 229 cases of acute pancreatitis treated between the years of 1941 and 1954. Kirby et al[9] reviewed the records of 110 patients with acute pancreatitis treated from 1946 to 1953. They compared this group with a series of 80 patients treated during the preceding 25-year period. The mortality rates of those with acute hemorrhagic pancreatitis decreased from 76.2 to 33.3 per cent, with acute edematous pancreatitis from 11.9 to 4.6 per cent, and with the idiopathic type of pancreatitis from 28.8 per cent in the earlier series to 13.8 per cent in the more recent group. A significant difference is seen in the three types. There seems to be a gradual improvement in the results of therapy during recent years. This diminution in mortality rate reflects the awareness of physicians for the disease and advances in diagnosis and therapy. With increasing numbers of patients surviving an attack of acute pancreatitis, complications and sequela are expected. Surgical assistance might be required.

The attack is frequently associated with a violent symptom-complex which simulates the numerous abdominal emergencies: acute cholecystitis, intestinal obstruction, perforations and penetrations of gastric and duodenal ulcerations,

acute gastritis, mesenteric thrombosis, and colonic diverticulitis. The diagnosis is often difficult to make and not infrequently two entities might be present, one of which is acute pancreatitis. When laparotomy is undertaken in search of a diagnosis or as the result of mistaken diagnosis, and acute pancreatitis is found, operative manipulation of the pancreas and the adjacent viscera involved in the inflammatory process is harmful. In this situation drainage of the peritoneal cavity and lesser omental sac is indicated and best accomplished with the use of the sump 2-arm airvent tube and a pump. Attempts to evacuate necrotic tissue in and around the pancreas are to be avoided. Incision of the pancreatic capsule and drainage of the organ is strongly contraindicated. The least trauma to the acutely inflamed pancreas is preferable. On occasions during such a laparotomy, biliary tract decompression by cholecystostomy or choledochostomy is a consideration. Removal of gallbladder calculi when present might be included. The theoretical basis is the interruption of bile reflux and the reduction of intraluminal choledochal pressure, a factor which might favorably influence the course of pancreatitis by relieving pancreatic duct obstruction. While often impossible to determine at the time of operation with the marked surrounding inflammatory process, the cause of the acute attack could be due to obstruction at the ampulla of Vater. The continued decompression might also prevent early relapses and the advancement of the pathologic process. When the acute attack has subsided, the cholecystic or choledochal catheter is used for cholangiography. During recent years a few cases treated in this fashion have been reported[8,10]. Re-evaluation of operative therapy in conjunction with modern medical treatment is in order. Experience with this approach will determine the ultimate usefulness of surgery during acute pancreatitis.

Acute pancreatitis was found in 29 or 18 per cent of 163 cases of acute cholecystitis[12,13]. The pancreatic inflammatory process is rarely extensive and the severity does not correspond to the level of the serum amylase. When an acutely inflamed gallbladder is present, whether the serum amylase is elevated or not, surgery is indicated in much the same manner as it would be without the associated pancreatitis. Early surgical intervention in acute cholecystitis has been advocated by many. Cholecystectomy appears to have a favorable influence on the course of pancreatitis, especially when calculi are present. The actual definitive surgery will depend upon the findings. With minimal pancreatic involvement, cholecystectomy is undertaken. With the patient's condition poor and pancreatitis present, the less extensive cholecystostomy is the procedure of choice. Upon recovery the cholecystostomy tube may be used for cholangiography. If cholecystectomy is performed, without choledochal exploration, the cystic duct stump may be used for insertion of a catheter, decompression, and study of the common bile duct at a later date. The usual indications for common bile duct exploration also apply provided the general condition of the patient is satisfactory. The finding of a dilated choledochus, the presence of or history of jaundice, palpable choledochal calculi, or multiple small calculi in the gall-

bladder, is an indication for choledochotomy, exploration, and T-tube drainage. Operative trauma to the mildly inflamed pancreas must be kept to a minimum. Postoperatively, medical management of the associated pancreatitis is advisable. Sanchez-Ubeda et al[15] reported 29 cases of acute cholecystitis and acute pancreatitis. They found gross pancreatic changes not impressive. Cholecystectomy was carried out in all patients and choledochostomy in 20 of the 29 cases. They found no increase in morbidity or mortality.

Occasionally the digestive inflammatory necrotic process spreads and dissects in various directions around the pancreas and in the retroperitoneum. A site of fullness, edema and fluctuation might be detected. The process, which occasionally becomes purulent by superimposed infection, requires adequate incision and drainage. The recrudescence of fever during recovery from an acute attack often indicates the presence of such an abscess. Kirby et al[9] showed a significant number of deaths resulted from delayed hemorrhage due to erosion of vessels from infection and enzymatic action. Subphrenic suppuration, with extensions into the mediastinum and pleural cavities, has been reported. Similarly, lesser sac accumulations of considerable magnitude necessitate drainage. This complication is found with the aid of appropriate roentgenograms.

Also as a result of the destruction of pancreatic and adjacent tissue by enzymatic inflammatory process, the localized collections form pseudocysts. The actual mechanism involved in the formation of pseudocysts is not entirely clear. These cysts appear clinically within a few days following the onset of an acute attack of pancreatitis or their presence may not be detected for weeks or months. They may occur in and about the pancreas, mostly in the lesser peritoneal sac, and vary greatly in size. The pseudocyst contains fluid which possesses a variable degree of enzymatic activity. There is no epithelial lining in these cysts. Most of the cysts following acute pancreatitis and traumatic pancreatitis are of this type. The management of pseudocysts will not be discussed in this paper. Spontaneous rupture of pseudocysts, however, which might occur during the acute phase has been reported and is worth mentioning. Occasionally the perforation follows trauma. A dramatic syndrome is characterized by the sudden onset of excruciating abdominal pain with shock usually of an extreme degree. Signs of generalized peritonitis are present. The recognition of the disappearance of a previous mass is of diagnostic aid. Abdominal tap might be helpful in establishing the diagnosis. Although only a few of these cases have been presented it is known that the mortality rate is high, around 60 per cent. Prompt diagnosis and vigorous treatment of the shock followed by laparotomy are required. Surgery is usually limited to simple drainage or marsupialization.

The coexistence of jaundice and acute pancreatitis often points out the need for surgery. Hepatic disease, cirrhosis and hepatitis, and hemolytic processes due to transfusion reactions and bacteremia or septicemia, account for the concomitant icterus. Not uncommonly the cause of jaundice is obstruction of the common bile duct by calculi. Icterus occasionally appears during the course

of an episode of acute pancreatitis, usually three to ten days after the onset of acute symptoms. By encroachment the pancreatic inflammatory enlargement gradually causes compression and obstruction of the common bile duct. Medical management is advisable for this type of icteric acute pancreatitis.

Of primary importance is the establishment of the diagnoses, which may be difficult since the signs and symptoms of acute pancreatitis are present as well as the findings related to the underlying cause of jaundice, provided the cause is not pancreatitis. In general the extrahepatic obstructed jaundiced patient with pancreatitis exhibits a clinical course which is acute, severe, associated with colicky upper abdominal pain, nausea, vomiting, chills and fever. Often there is a history of long-standing gallbladder disease. The laboratory findings are those of obstructive jaundice and acute pancreatitis. The degree of icterus is often high. The heptocellular icteric case follows a more gradual course with abdominal pain, anorexia, flatulence, indigestion, weight loss, often hematemesis and melena. Hepatomegaly and ascites are occasionally present. Many of the latter group are alcoholics and have been icteric for weeks or months prior to the acute illness. Among the laboratory findings are those of liver parenchymal damage, a reversed A/G ratio with reduced albumin and increased globulin, decreased total serum protein, increased retention of bromsulfalein, increased cephalin flocculation, thymol turbidity, and serum alkaline phosphatase.

With a careful examination and laboratory aid, the diagnoses are accurately made and proper treatment is instituted. The therapy is directed at both entities, acute pancreatitis and the jaundice. If the jaundice is thought to be due to obstruction of the common bile duct, except when due to pancreatic inflammatory enlargement, surgical decompression of the biliary tract is indicated. If the patient's condition is poor and the pancreatitis severe, decompression by the least traumatic method, cholecystostomy, is performed. The jaundice is thus relieved. Obstruction of the pancreatic duct might also be relieved by removing the intraluminal choledochal pressure. If the pancreatitis is found to be mild and the surrounding inflammatory process not great, exploration of the common bile duct and choledochostomy are included. The peritoneal cavity is also drained during the procedure. When the acute process has subsided, the choledochus is visualized roentgenographically. Other procedures depending on the findings may then be planned.

The preoperative preparation of these patients requires prompt replacement of electrolytic losses of sodium, potassium and calcium, correction of the blood volume deficit with serum albumin, 300 to 500 c.c. daily for 3 to 5 days, or plasma expanders such as dextran, the liberal use of Vitamins K, C and B, correction of anemia with blood transfusions, broad-spectral antibiotic therapy, continuous nasogastric suction, anticholinergic drugs, and the relief of pain with Demerol. Morphine and codeine are not used since these drugs cause spasm of the sphincter of Oddi.

Summing up, acute pancreatitis is a disease which causes numerous medical and surgical problems. The presenting snydrome often provides a difficulty in differential diagnosis. Laparotomy during the acute phase is indicated when the diagnosis is in doubt. When acute pancreatitis is found, the operative procedure is usually limited to peritoneal drainage. With associated cholecystitis and cholelithiasis, cholecystostomy or cholecystectomy is a consideration. On occasions choledochostomy may be included. Surgical intervention is also indicated for complications of acute pancreatitis, retroperitoneal, intraperitoneal, dissecting inflammatory processes, collections, and abscesses. The surgical approach is used occasionally, when jaundice due to choledochal obstruction is associated with acute pancreatitis.

Dr. Ross:—The next speaker will be Dr. Greaney, who will give us a few thoughts on the late effects of pancreatitis of the chronic or relapsing type.

Dr. Edward M. Greaney, Jr.:—The term "relapsing" pancreatitis has come to mean a clinical syndrome characterized by acute recurrent attacks of pancreatitis superimposed upon a previously diseased gland. Actually there is not a continuing pathological process, as the term would imply, but damage over a period of years by acute recurrent attacks, usually in an alcoholic patient.

The average surgeon's experience with this form of disease is necessarily limited. Treatment is mainly medical. The surgical treatment has come to be almost an institutional situation. A good many of these patients are products of long-term illness, long-term alcoholism, repeated medical-surgical failures, and are of lower economic status.

The etiology of this disease, of course, is still obscure, with several factors probably having some significance. One of the most significant is alcoholism. Actually it is difficult to make the diagnosis with certainty unless alcoholism is a factor.

Associated biliary tract disease, as an etiologic agent, has been indicated and if it is present carries with it a more favorable prognosis. Other more remote causes for pancreatitis should be ruled out as should the occasional case which is associated with hyperparathyroidism, or with the familial form of the disease, and also the traumatic case.

The morbid anatomy involved in this disease varies from edema to frank necrosis, depending upon what stage of the disease is met. Gland destruction is a prominent feature in varying degree resulting in the destruction of the exogenous and endogenous function. Ductal stenosis and dilatation can be demonstrated both on the anatomy table as well as at the time of surgery.

Pseudocyst is a common cause of symptoms in the chronic form and is found in a significant number of cases.

The clinical manifestations of the disease also vary. The pain is of such an intense nature that it leads to either narcotic or further alcoholic addiction and it is a very difficult thing to evaluate.

The pain persists between the episodes of acute attacks. Diabetes may be present, in the burned out gland, as well as steatorrhea. If a pseudocyst is formed there may be pressure upon adjacent organs with a palpable mass in the abdomen. There may be complete or incomplete intestinal obstruction. Associated with the pancreatitis may be gastrointestinal hemorrhage in the chronic form of the disease. Particularly is this true in pancreatic calcinosis. Jaundice may be present due to the obstruction of the common bile duct. Pancreatic dysfunction may also be present with its sequela of weight loss, anorexia and vague digestive symptoms.

The surgical attack on the gland has taken several forms over the years. There is no good attack surgically on this disease, no attack that will result in uniformly good results. Dr. Pierre Mallet-Guy of Paris has recommended sympathectomy in the treatment of this disease, reporting a large percentage of good results. He feels it does away with pain as well as diminishing secretion of the glands. In this country these results have not been duplicated.

Vagotomy with drainage has been advocated and more or less abandoned. Attacks on the gastrointestinal tract are notoriously poor in results except in the specific case of the penetrating duodenal ulcer which is the cause of the pancreatitis. Attacks on the biliary system, if there are associated gallstones or common duct stones, may give excellent results in the patient who is not an alcoholic.

Attacks on the sphincter mechanism have been extensively studied by Dr. Doubilet and his group with beautiful diagrams and pressure studies. Many centers cannot duplicate their results, however, and not everyone accepts his recommendations. An attack on the sphincter, however, is usually made first in these patients as it is a less dangerous procedure than resectional pancreatic surgery.

The direct attack on the gland may be a resection of the head of the pancreas and body as advocated by Dr. Cattell or a resection of the tail only. Resection of the tail carries with it a lower mortality and lower morbidity. Dr. Cattell reports 8 cases with 5 very good results. Pancreatic or duodenal resection is reported as a last resort also.

Decompression of the pancreatic ductal system has been advocated by Dr. Duval and others. This involves anastomosis of the jejunum to the major pancreatic duct of Wirsung, with or without resection of the tail of the pancreas.

Another procedure advocated by Dr. Ralph Bauer's group is reimplantation of the common bile duct to the jejunum. Dr. Waltman Walters of the Mayo

Clinic has also used this in reimplanting the common duct in the stomach. Dr. Cannon of U.C.L.A. has done several cases of ductal ligation with equivocal results.

As you can see the multiplicity of forms of attack mean that there is no one good single surgical treatment.

Dr. Frieden:—There are approximately in association about 50 per cent of cholecystitis and acute pancreatitis. The series of autopsy material runs somewhere between 50 and 70 per cent. It is a very high percentage of coexistence.

Frequently it is stated that cholecystitis and cholelithiasis are causes of pancreatitis. Actually, I think a basic cause of cholecystitis, cholelithiasis, and pancreatitis is obstruction and stasis in these continuous ductal systems. The sphincter of Oddi is common to the extrahepatic biliary and pancreatic ducts. Obstruction at the sphincter caused by reflex spasm, calculi or other lesions might produce stasis and the diseases concomitantly. The presence of cholecystitis, by causing reflex sphincter spasm and pancreatic duct obstruction, is considered a factor in the pathogenesis of pancreatitis. Occasionally calculous obstruction at the sphincter of Oddi from cholelithiasis is also the cause of pancreatic duct obstruction and pancreatitis.

Dr. Ross:—In the interest of time I will run along to the next question: Dr. Guth, how does biliary disease cause pancreatitis?

Dr. Guth:—That is a controversial point. There are several theories. Dr. Farris described the common channel theory. According to this theory a stone blocking the ampulla of Vater would permit a common channel to form, and bile could flow into the pancreatic duct. This results in activation of pancreatic trypsinogen and the development of pancreatitis.

There are several arguments against this theory, one being that when bile is injected into the pancreas under normal pressure—not under excessive pressure—pancreatitis does not result. It only results when the bile is injected into the pancreas under increased pressure.

Secondly, under normal circumstances the secretory pressure in the pancreas is somewhat higher than that in the gallbladder, so, if anything, one might expect the flow to be the other way. But there are arguments pro and con.

Dr. Ross:—We might get the matter of the common channel cleared up a little bit in our own minds. We have heard so much about it before, and we thought reflux of the bile was the cause of pancreatitis. We now know that that reflux of bile occurs in almost every one of us, and no pancreatitis develops.

I would like to elaborate just a little bit on what, then, causes this. What is the influence, Dr. Farris, on contaminating the bile with intestinal contents by a reflux from the intestines, from a loose sphincter, for instance?

Dr. Farris:—I think, as I mentioned earlier, it is a mistake to try and consider the biliary duct system as apart and a separate entity from the pancreatic duct system. If you inject one duct system with methylene blue and bacteria I am positive you can demonstrate methylene blue or bacteria in the other duct system. I know from personal experience that the vast majority of patients with common duct obstruction have an academic form of pancreatitis. When you examine the head of the pancreas it is thickened and sometimes mistaken for carcinoma.

In patients with acute cholecystitis a blood amylase will sometimes be misleading. It frequently will show rather large elevations. I saw a patient just a month ago, hospitalized with pain and slight jaundice, and preparations for exploration were running along very smoothly. A blood amylase, however, was taken and reported as 700 clinical units. Everybody said, "This man has pancreatitis; we had better lay off." He was in the hospital six weeks and finally got well. Ultimately we operated on him and removed the stones in the common duct which should have been removed in the first instance.

The point I make is that most people with biliary duct disease do have an academic form of pancreatitis. It may not be the dramatic classic picture you are all looking for. If the bile is injected into the pancreatic duct system by itself, it does not produce pancreatitis. If, however, it is mixed with bacteria under elevated pressure, you will frequently produce pancreatitis.

So, in answer to your question, when the intestinal content contaminates the bile, normally the pancreatic pressure is a little higher than the biliary duct pressure. After an enormous meal or after an alcoholic debauch you may get higher pressures in the biliary duct system. Also the duct of Santorini, emptying out independently into the duodenum, offers a decompression of the pancreatic duct sysem. The duct has no ampulla, has no sphincter, so theoretically there should be no pressure in the pancreatic duct system whatever, and I am confident that maybe a third of the cases of pancreatitis are caused by reflux of bile, and I am also confident that most people who have obstruction of the common duct or infection of the common duct, if you look carefully enough, also have pancreatitis.

Dr. Ross:—We may all agree that the old theory of refluxing of bile is of no value, but if it is contaminated with infection, or concentrated bile acids, or some other factor arises, or there is a great increase in the pressure of it, we may get pancreatitis.

Dr. Greaney mentioned alcohol. I think that is important to emphasize. Would you elaborate on that a little bit, Dr. Greaney?

Dr. Greaney:—Well, the classical cases, of course, almost uniformly have an alcoholic history, and in cases of acute pancreatitis almost always have alcohol as a factor. Alcohol is just one of the many factors that will raise the

secretory pressure in the pancreatic duct, as has been shown by Doubilet in his series. This is just one factor. Psychic factors have been shown to increase the pancreatic duct pressure, including vascular spasm. Any one or a combination of all of these may result in these acute attacks.

Dr. Ross:—We will have to hurry and make these answers snappy and short.

I am told that the taking of food, ordinary food, into the stomach and duodenum doesn't necessarily increase pancreatic flow, but alcohol has a tremendous effect. Would you say a word about that, Dr. Guth?

Dr. Guth:—Alcohol, as you know, is a very potent stimulant of gastric secretion. As Dr. Farris indicated in his talk, when gastric hydrochloric acid reaches the duodenal mucosa, the hormone secretin is released. Secretin is a very powerful stimulant of pancreatic secretion.

Dr. Ross:—We have heard some mention of vascular factors producing pancreatitis. That is a new thought, I am sure, in recent years, and I would like to have just a brief discussion on that, Dr. Frieden.

Dr. Frieden:—Pancreatitis experimentally can be produced in many ways. That is why it is such a highly controversial issue. We could argue about it all morning.

Popper, in his experiments several years ago, introduced the fact that if one obstructs the duct he will not get a violent pancreatitis, but then ligation of some of the major vessels of the pancreas would produce it. In postoperative acute pancreatitis we feel this situation is often a factor.

Dr. Ross:—Thank you very much.

Are there any hereditary factors, Dr. Guth, in the production of pancreatitis?

Dr. Guth:—Recently that has been described, as Dr. Greaney mentioned. There have been families in which several members all suffered from a chronic relapsing form of pancreatitis. When these families were studied metabolically it was found that there was an increased secretion of certain amino acids in the urine, primarily lysine. The significance of this is not as yet understood, but it has been theorized that possibly some abnormality in amino acid metabolism gives rise to a situation predisposing to pancreatitis.

Dr. Ross:—Dr. Farris, would you comment on how a duodenal ulcer causes some pancreatitis?

Dr. Farris:—As I mentioned, duodenal ulcer in the posterior wall may actually destroy the wall and invade the pancreas and produce sequential events similar to pancreatitis. As a matter of fact, I have seen duodenal ulcers that have actually penetrated the pancreas to the extent that they have communicated with the biliary duct system.

Also, people with duodenal ulcer, and also with gastric ulcer, have a so-called diathesis with hypersecretion of gastric juice of low pH which produces abnormal amounts of secretin, with accompanying excessive amounts of pancreatic secretion.

Thirdly, it is true that certain people with gastric ulcers and duodenal ulcers who have had gastric resection may also have chronic recurring pancreatitis and after gastric resection never have another attack of pancreatitis.

Dr. Ross:—Then, Dr. Greaney, have you heard or have you any knowledge of pancreatitis occurring in other diseases, such as hyperthyroid?

Dr. Greaney:—Yes, sir. Dr. Selye has indicted the pancreas as being one of the so-called stress organs. It is an attractive theory, and pancreatitis has been seen in the course of many of the diseases, which include parotitis. Recently Dr. Oliver Cope and Dr. Hardy described it in the course of hyperparathyroidism; it has been described in the course of ulcerative colitis; it has been described in the course of duodenal ulcers and in the course of almost any other disease you want to mention. One of the most recent was in the hyperparathyroid.

Dr. Ross:—Dr. Frieden, you have mentioned postoperative pancreatitis. Would you very quickly enumerate what are the causes of acute pancreatitis occurring after a postgastric resection?

Dr. Frieden:—In studying the causes based on experimental work of others, I am fairly well convinced that pancreatic duct obstruction is an important factor in the cause of pancreatitis. That being the case, trauma to the head of the pancreas produces edema, and if one remembers about the termination of the pancreatic duct and the common bile duct, as has been beautifully shown by a number of investigators—Reinhoff, Stirling, Wels and Kernutt—these narrow down to less than one mm. in diameter. With the addition of edema there is a very good set of circumstances to produce obstruction. Also in this anatomical set-up there is a projection of pancreatic tissue which actually extends in between the two terminations. Thus with edema, compression of the termination of the pancreatic duct is the result.

Many cases of pancreatitis following surgery are produced by such factors as ligations of vessels, ligation of the duct itself. Stress has also been implicated by Ivy. He called it a parasympathetic pancreatitis. The stimulation caused duct obstruction, congestion, and a set of circumstances which might produce pancreatitis. I have seen it as part of a totally unconnected surgical procedure, such as thyroidectomy and cecostomy.

Dr. Ross:—Now we would like to concentrate a little more on the handling of acute pancreatitis and chronic pancreatitis, and I would like to ask Dr. Guth, what is the value of the amylase test, and how accurate is it, and how practical?

Dr. Guth:—The serum amylase determination is the most valuable laboratory procedure in the diagnosis of acute pancreatitis. Routinely most hospital laboratories use one of the modifications of the original Somogyi method.

There was an interesting survey made recently by the Los Angeles County Pathology Society in which they sent a sample of serum to some 45 laboratories in the Los Angeles-Orange County area. They spiked this serum with amylase, so it should read somewhere between 400 and 500 Somogyi units. They got answers back from about 27 of the laboratories, and the answers ranged from about 100 to 1,100 units. The results were so fantastic that a brochure was sent out about it. They are now looking into why there should be this tremendous variation.

That points up one thing: the importance of knowing your own laboratory and the results obtained with different tests.

Dr. Ross:—We have a case before us of acute pancreatitis. Dr. Farris, would you quickly tell us what you think about the differential diagnosis?

Dr. Farris:—I will say I am never confident of the diagnosis of acute pancreatitis. I am not sure he hasn't a perforated ulcer, acute appendicitis or intestinal obstruction. I place very little reliance on the amylase. I restrain myself from ordering it. I don't like to be misled. I have seen tragedies occur where people with acute surgical abdomens were treated for acute pancreatitis and they had something else.

I have no hesitancy in operating upon a patient. I am speaking controversially, I know, but if there is any question I would rather get inside his abdomen to be sure he doesn't have acute cholecystitis, and if I find pancreatitis I think draining his gallbladder will do him a great deal of good (as well as temporary gastrostomy).

Dr. Ross:—That brings up a question to my mind. We are faced with this acute attack of pancreatitis and we have been taught for years that medical management certainly gives the lowest mortality, yet we are hearing today about surgery doing the task.

First of all, I would like to ask Dr. Greaney how he combats the pain in pancreatitis.

Dr. Greaney:—First of all I would like to say that I worry as much as Dr. Farris, but I do get an amylase, because I consider it not a reason to stay out, but a reason to explore the common duct if I find cholecystitis.

We have in the past, as Dr. Farris has suggested, used ganglion blocking agents, which didn't really prove valid. I know sympathetic block has been used, but certainly not under my direction or anywhere where I have worked with any degree of success. So for control of pain, morphine or its derivatives is still the best.

For the control of shock, this involves replacement of either plasma or whole blood, because this patient's circulating blood volume has been diminished by setting up of the so-called third compartment. To quickly answer it, I would give the patient whole blood and/or plasma.

Dr. Farris:—I meant to say also that I think the intraperitoneal tap is a valuable aid in the diagnosis. If you tap his abdomen and get sterile bloody fluid and send that to the lab and it comes back significantly elevated you are on safe grounds.

Dr. Ross:—Dr. Frieden, if you operate for acute pancreatitis and you open the common duct, do you use the long Cattell tube or not?

Dr. Frieden:—No, I do not. There have been several cases in which we think the use of the tube has caused pancreatic duct obstruction and hemorrhagic pancreatitis.

Dr. Ross:—We will presume that a case of pancreatitis under medical care is not doing well, and there are some indications for operating later. What other things can happen?

Dr. Farris:—Abscesses. There have been a couple reported in the mediastinum.

Dr. Ross:—And there are some late complications of pancreatitis, Dr. Guth, such as diabetes, pancreatic fistulas, and recurrent pancreatitis. I believe that is true?

Dr. Guth:—Yes.

Dr. Ross:—Shall we say that if patients refrain from using alcohol it is sometimes stated that they may not have any more acute attacks of pancreatitis, but sometimes they do go into the chronic or relapsing stage? In the interest of time we will say that the diagnostic methods are similar to those carried out in the acute stage. I think Dr. Guth would probably talk about malnutrition and all that sort of thing. What x-ray studies would be of any value here? Dr. Greaney?

Dr. Greaney:—X-ray studies would include a flat film of the abdomen, an upper gastrointestinal and a lower gastrointestinal, to ascertain the status of the duodenal loop and displacement of adjacent organs.

Dr. Ross:—The medical treatment, of course, is paramount here again, because some of them do get along fairly well on medical care. But on the whole, most of them come to surgery eventually. Supposing you are operating on a case of prolapsing pancreatitis. What is your main or preferable way of approaching it?

Dr. Frieden:—As in many other medical problems, I think we ought to stage this disease, because there is a very great variance in the underlying

pathologic process. The type of pancreatitis which goes along with alcoholism, a chronic interlobular fibrosis, is coexistent with the liver disease of alcoholism. They go hand in hand. We know that about 40 per cent will have recurrent attacks after an acute attack. In the early stage, I think the disease is in the main due to obstruction of the pancreatic duct at the termination. The procedure would be first to clear the gallbladder as a possible cause. Once the biliary tract is cleared, after that I think sphincteroplasty deserves a chance. I think we should try to break up any possible obstructive mechanism. With sphincterotomy one does not render the sphincter incompetent. The sphincteric incision heals well, and I cannot possibly see how one might get far-reaching results with sphincterotomy. Sphincteroplasty with wedge excision and mucosal approximation is preferred.

Frequently by decompressing the obstructed dilated ductal system such as with pancreatojejunostomy, one might get favorable results. I hold off pancreatic resection as the very last approach. Powers, in an animal experiment, showed that obstruction plus a number of factors, was a cause of pancreatitis. With the obstruction relieved no pancreatitis was found.

Dr. Ross:—Dr. Farris, when you find, in chronic pancreatitis, stones in the duct, what is your approach to that?

Dr. Farris:—I think I should make an attempt to remove them. I have, as a matter of fact, on two occasions. Frequently the duct is like cement; it is not a solitary calculous. I think the logical approach is distal removal of the pancreas and anastomosis to the jejunum.

I think it should also be said that you approach the problem slowly and use the simple things first, and pancreatectomy should be reserved for the patient who has had everything else.

Dr. Ross:—Dr. Greaney, supposing there was a generalized distribution of small stones. What would you do then?

Dr. Greaney:—That would involve the burned-out gland with necrotic processes throughout the gland, and I would think then, if this patient came to surgery, from my review of the literature, at least, he should have a pancreatic duodenal resection, preferably at the hands of a man who has done many, like yourself.

Dr. Farris:—Where the duct is pretty well obstructed, with calcification, and x-ray shows diffuse calcification throughout the whole gland, and the patient has had three operations already—gallbladder, vagotomy, and pyloroplasty—and still has pain, what would you do?

Dr. Ross:—The big factor here is terrific pain, which is unbearable, and I have felt in the past that a total pancreatectomy is about the only thing to do. Recently, however, it has been suggested that the whole duct, from the tail

right to the head, should be widely opened up, and then take a piece of jejunum and thread the pancreas into the open mouth of the jejunum. It is hoped that by relieving the pressure in this manner the pain and disability would be relieved. This is a newer method and only a few cases have been done, so we do not know how to evaluate it, but presumably, if this is not successful, the last resort would be a total pancreatectomy.

I think retrograde drainage is a very excellent thing. It has been suggested in the more minor cases that there are two methods of doing that. One is to cut the pancreas off and put the end into the end of the jejunum; others favor lateral anastomosis being done.

Pseudocysts have been mentioned many times in the discussion, and we would like to know a few things about pseudocysts. Are these pseudocysts lined with secreting membrane? Do they contain ferments?

Dr. Guth:—The pseudocyst actually forms from destruction of the pancreatic gland itself by the digestive action of the pancreatic enzymes with the formation of a sterile abscess. It doesn't actually have a wall of epithelium around it. It can, though, contain pancreatic ferments, because it may be connected with one of the branches of the pancreatic duct.

Dr. Ross:—Dr. Frieden, if you were presented with a pseudocyst, how would you handle it?

Dr. Frieden:—I think the presence of a pseudocyst is an indication for surgery.

There are various routes. At the present time I think internal drainage is entirely acceptable, and by that I mean simply applying a loop of jejunum to the cyst in a side-to-side manner. This method is perhaps the best of the surgical procedures. On occasion simply bringing the cyst up to the external abdominal wall is effective.

One has to be certain of the diagnosis, and occasionally you may be dealing with a cyst adenoma or cyst adenocarcinoma, and then the approach is different.

Dr. Ross:—I think Dr. Frieden brought out a very important point. When you see a cyst, it should be opened and inspected inside because you might be dealing not with a simple type of cyst, but a cyst adenoma, so you would not do well with simple drainage. It would keep on growing and cause you difficulty later.

Dr. Farris, would you ever drain a cyst into the head of the duodenum? Is that a feasible thing?

Dr. Farris:—I think so. I would be more inclined to drain it into the stomach.

Dr. Ross:—Drainage into the stomach is another way which seems to be quite satisfactory.

I might summarize with a few words that the pancreas is a very formidable organ; it is a mysterious organ involving important physiochemistry and pathological problems. We do not understand it fully, but we are learning all the time.

We may conclude also that alcohol is a very important element in the causation of pancreatitis. I have heard it stated that you can't do a thing with a patient unless he will stop drinking. I think it is most important to emphasize that to the patient.

Dr. Guth has given us the usual simple tests and he elucidated on many new tests. Only time will tell us how important these are. I think it is important for us all to learn these new tests, and from time to time, put them into practice.

I think we are changing our attitude toward acute pancreatitis. We felt in the past that medical care was predominant, but we know now, that there are certain surgical indications for an operative approach. These have been discussed today.

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THE DUAL ROLE OF THE ADRENAL GLANDS IN THE PATHOGENESIS OF PEPTIC ULCER

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Since the use of corticosteroids in the treatment of various medical problems it has been found that a common complication of this therapy is the reactivation of preexisting peptic ulcer, or the production of a new ulcer with the possibility of hemorrhage or perforation. This has led to the concept that the adrenocortical steroids play a fundamental etiologic role in peptic ulcer disease. The mechanisms by which the adrenal cortical hormones induce peptic ulcer is thought to be the possible stimulating effects of these substances on the gastric secretion of acid and pepsin.

The studies of Gray and his collaborators[1] have demonstrated increased gastric activity following the administration of corticotropin or adrenal glucocorticoids as evidenced by increased secretion of hydrochloric acid and pepsin, as well as increased excretion of urinary uropepsin. Vagotomy did not appear to alter the gastric response to corticotropin, indicating the absence of neurogenic control. Similar results have also been obtained in experimental animals by Zubiran and his collaborators[2].

It has also been observed that in patients with adrenal insufficiency (Addison's disease) there is a decrease in gastric acid and pepsin secretion[3], and adrenal steroid replacement therapy restored the gastric secretory activity[4]. In patients with adrenal hyperactivity (Cushing's disease), however, there is an increase in gastric acid and pepsin secretion, and following adrenalectomy there is a return to normal or subnormal levels[5].

The rarity of chronic peptic ulcer in patients with Addison's disease has been reported by various investigators, and appears to be associated with a decreased gastric secretion of acid and pepsin. On the other hand gastric or duodenal ulcers develop in Addison's disease during corticosteroid replacement therapy, accompanied by an increase in gastric secretion of acid and pepsin[4].

In view of this evidence the intimation is strong that adrenal cortical overactivity (hypercorticism) may be concerned in the pathogenesis of peptic ulcer.

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This is, however, in very sharp contrast to the fact that in Cushing's disease, which is the disease of natural hypercorticism, peptic ulcer is rarer than seen in the general population[5,6]. The low incidence of peptic ulcer in Cushing's disease would tend to diminish the possibility of adrenocortical hyperfunction alone as a primary mechanism in the usual peptic ulcer. There must be another factor present.

It is difficult to believe that the digestive action of acid and pepsin would produce a round punched-out lesion. Virchow, in 1893, expressed the opinion that only a local cause could account for a localized lesion such as a round peptic ulcer. Before a peptic ulcer reaches the stage of chronicity it must begin as an acute ulcer and acute ulcers are often found in areas along the gastrointestinal tract where there is an absence of acid and pepsin. Acid and pepsin are not necessary in initiating an ulcer but they do play an important role in converting an acute ulcer into a chronic ulcer.

Long before the use of corticosteroids it has been known that there was a relationship between acute ulcers of the stomach and hypoadrenalism. There is ample evidence in the literature that damage to the adrenal glands is accompanied by a high incidence of ulcerative lesions in the gastrointestinal tract. In 1916, Mann[7] first noticed acute ulcers in adrenalectomized animals. He showed that lesions developed in the stomach and duodenum in approximately 90 per cent of animals that died of adrenal insufficiency as the result of removal of both adrenal glands. McLaughlin[8] found that when the adrenals were not removed but were merely damaged by high frequency coagulating current, 17 of 21 animals had definite acute ulceration of the digestive mucosa. In the human, multiple acute ulcers are found along the gastrointestinal tract with adrenal insufficiency during the Addisonian crisis, although chronic peptic ulcer is exceedingly rare in Addison's disease.

Before the discovery of cortisone, adrenal cortical insufficiency was a relatively rare condition, but since the therapeutic use of highly active corticosteroids its frequency has greatly increased. Administration of adrenocortical steroids, particularly in fairly large amounts and over a long period of time, is known to depress adrenocortical function. Following withdrawal of the exogenous adrenocortical hormones, a state of relative adrenal insufficiency exists, and if a patient is faced with some stressful situation, the adrenal gland will be unable to respond to it.

Stress increases the consumption or utilization of corticoid hormones by the tissues and the resulting decrease in their blood-level causes a discharge of corticotropin by the pituitary which stimulates the adrenals to secrete more corticoid hormones. If, however, the adrenal is unable to respond to corticotropin because of adrenal damage or exhaustion, the overwhelming stress with secondary adrenal insufficiency may produce acute ulcers on the basis of shock, accompanied by hypotension, hemoconcentration, vascular stasis, capillary fra-

gility, leading to focal mucosal hemorrhages. These focal mucosal hemorrhages may eventuate in hemorrhagic erosions and acute ulcers. When the mucosal hemorrhage is very close to the surface, the thin injured epithethial layer covering may be rubbed off or swept away by the gastric contents passing over it leaving a hemorrhagic erosion, which in turn becomes an acute ulcer when the hemorrhagic contents is wiped away or digested. Other mucosal hemorrhages become absorbed and disappear. Schindler[9] reported interesting observations on the incidence of gastroscopically observed focal mucosal hemorrhages and hemorrhagic erosions in perfectly normal stomachs. He stated that the transition

TABLE I

CHANGES IN THE ADRENAL GLANDS ASSOCIATED WITH ACUTE GASTROINTESTINAL LESIONS

Adrenal gland	Total no. of cases	Cases of ulcer	Cases of focal hemorrhage	Incidence of adrenal changes and G.I. lesions
No microscopic abnormalities	439	39	45	19%
Mild changes: Congestion Round cell infiltration	482	87	46	27%
Severe changes: Hemorrhage Necrosis Thrombosis Tuberculosis Leukemic infiltration Atrophy and fibrosis Tumors	181	43	41	46%
Totals	1102	169	132	

of some of the mucosal hemorrhages to hemorrhagic erosions and to acute ulcers may be observed if patient is gastroscoped at frequent intervals.

Mucosal hemorrhages and acute ulcers are also found during the shock phase of the alarm reaction. Selye[10] has postulated that any systemic stress, such as burns, trauma, surgery, etc., will evoke an alarm reaction in the organism. The alarm reaction is subdivided by Selye into the shock phase and the countershock phase. During the shock phase hypocorticism exists and mucosal hemorrhages and acute ulcers may form. This is followed by the countershock phase during which there is a stimulation of adrenal cortical hormone by the corticotropin discharged by the pituitary, and producing hypercorticism.

After an acute ulcer develops during adrenal insufficiency, it begins to heal as soon as the initial injury occurs. If, however, exogenous hypercorticism exists due to the administration of large amounts of corticosteroids, or if endogenous hypercorticism exists due to the stimulation of adrenal cortical hormone by corticotropin, two effects take place: 1. an increase in the gastric secretion of hydrochloric acid and pepsin, and 2. by the anti-inflammatory action, an inhibition of fibroblast proliferation during wound healing and a delay in the formation of granulation tissue. As a result the acute ulcer may become deeper leading to hemorrhage or perforation, or healing may be retarded causing it to go on to chronicity (Fig. 1).

Since acute ulcers are probably not often diagnosed clinically unless there is some dramatic manifestation such as hemorrhage or perforation, it is impos-

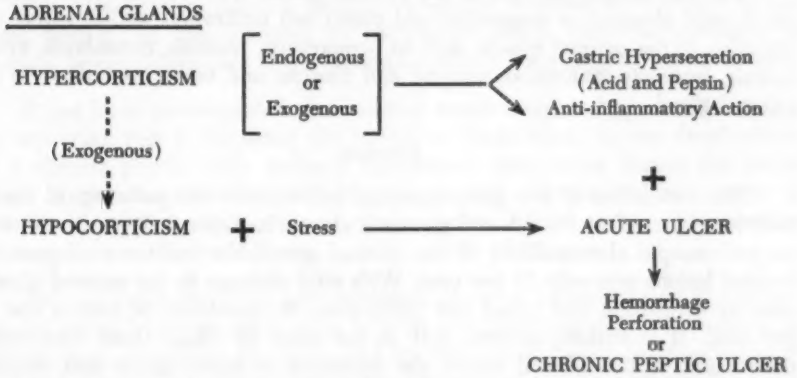

Fig. 1—The dual role of the adrenal glands in the pathogenesis of peptic ulcer.

sible to give an accurate estimate as to how frequently they occur. They are much more common than is generally supposed. It is very difficult to gather evidence of acute ulcers because they heal very promptly, usually without leaving a trace, they are difficult to demonstrate by roentgen examination, and are seen only when the stomach is inspected by gastroscope, at operation or at necropsy.

Selye[11] has shown that these gastrointestinal ulcers which occur during the shock phase of the general adaptation syndrome, are seldom found in clinical cases, because the gastrointestinal tract is rarely inspected during or soon after the shock phase. If, however, the stressor happens to be a fatal illness or a fatal traumatic condition, then the necropsy material should reveal focal mucosal hemorrhages, hemorrhagic erosions and acute ulcers of the gastrointestinal tract, especially if death occurred soon after the shock phase of the alarm reaction. The necropsy findings would also show the relation of these acute gastrointestinal lesions to adrenal damage. This study was undertaken with this point in view.

Material and Method

Our material was drawn from 1,150 consecutive autopsies at St. Luke's Hospital, Cleveland. Of this total number of necropsies, 48 were not considered in this report because of restricted autopsy in which the adrenals were not examined. Thus there were 1,102 cases in which detailed study was made.

This study concerns the incidence of focal mucosal hemorrhages, hemorrhagic erosions and acute ulcers of the esophagus, stomach and duodenum, and their relation to adrenal damage. That these lesions occurred before death and were not the result of postmortem changes was shown by miscroscopic study. Acute ulcers and focal mucosal hemorrhages were also found in the jejunum, ileum and colon, but are not discussed in this report.

The microscopic changes in the adrenal glands were studied and recorded as: 1. mild changes, as congestion and round cell infiltration, and 2. severe destruction of the adrenal glands, such as hemorrhage, necrosis, thrombosis, tuberculosis, leukemic infiltration, atrophy and fibrosis, and tumor metastasis to the adrenal gland.

Results

The correlation of the gastrointestinal lesions with the pathological abnormalities observed in the adrenal glands is shown in Table I. When there were no microscopic abnormalities of the adrenal gland, the incidence of gastrointestinal lesions was only 19 per cent. With mild changes in the adrenal glands, such as congestion and round cell infiltration, the incidence of lesions was 27 per cent. It is striking to note that in the cases in which there was severe destruction of the adrenal tissue, the incidence of acute ulcers and mucosal hemorrhages was 46 per cent.

The terminal pathological conditions may be considered the "stressors" that produced the alarm reaction described by Selye[10,11] during which the acute lesions developed. The incidence of acute ulcers and mucosal hemorrages was highest following such terminal conditions as severe burns, severe injuries, and postoperative cases.

The focal mucosal hemorrhages found in the necropsy material varied in size and in depth, the largest was 3 cm. in diameter. Some of them occurred very close to the surface of the mucosa. There were only 18 hemorrhagic erosions which we listed as acute ulcers.

Comment

It is evident from the present study that focal mucosa hemorrhages and acute ulcers of the gastrointestinal tract are much more common than has been realized and that they occur more frequently when there is evidence of adrenal damage.

The focal mucosal hemorrhages found in the necropsy material varied in size and depth. Some of them occurred so close to the surface of the mucosa that any trauma that may be produced by food or peristalsis could readily break the thin epithelial layer and convert the lesion to a hemorrhagic erosion. The number of hemorrhagic erosions were few, suggesting that most of them were converted to acute ulcers. The focal mucosal hemorrhages and acute ulcers were also found in the jejunum, ileum and colon, in the areas where there is an absence of acid and pepsin.

For every mucosal hemorrhage and acute ulcer that were found in prolonged stressful situations, we must assume that several more were present prior to necropsy, as many acute ulcers heal very rapidly and leave no trace, and many mucosal hemorrhages become absorbed and disappear.

Our investigation shows a striking correlation between the severity of adrenal damage, as demonstrated by microscopic study, and the incidence of mucosal hemorrhages and acute ulceration of the upper gastrointestinal tract.

It has been demonstrated that adrenal insufficiency or hypocorticism plays an important role in initiating the lesion, or acute ulcer, in the development of a chronic peptic ulcer. Adrenal insufficiency may occur during the shock phase of the alarm reaction following a stressful situation, or may occur as a result of suppression of adrenocortical function following the administration of exogenous corticosteroids over a long period of time.

Adrenal hyperactivity or hypercorticism plays an important role in converting the initial lesion or acute ulcer to a chronic peptic ulcer by suppression of inflammatory and repair processes, and by stimulating gastric hypersecretion of acid and pepsin. This occurs during the countershock phase of the alarm reaction when there is a discharge of endogenous cortiocotropin by the pituitary. Hypercorticism may also occur when a large amount of exogenous adrenocortical hormones are administered.

The processes of tissue destruction and tissue repair take place simultaneously and the acute ulcer may heal, may perforate or hemorrhage, or may go on to chronicity depending upon the balance between destruction and reparative factors.

The hormonal factors merely begin the chronic stage of a peptic ulcer, because the adrenal output gradually returns to normal following the countershock phase of the alarm reaction. Chronic emotional stress, however, may also be transmitted to the stomach by way of the neurogenic pathway involving the vagus nerve, and will continue the hypersecretion of acid and pepsin. This will further disturb the balance between destruction and reparative factors, and will prevent the ulcer from healing, thus continuing the chronic stage of a peptic ulcer.

Summary

Experimental and clinical evidence of the relation of systemic stress and adrenal damage to the development of acute ulcers in the upper gastrointestinal tract is reviewed.

In a series of 1,150 consecutive necropsies performed at Saint Luke's Hospital we found a striking correlation between the severity of adrenal damage, as demonstrated by microscopic study, and the incidence of focal mucosal hemorrhages and acute ulceration of the upper gastrointestinal tract.

The adrenal glands play a dual role in the pathogenesis of chronic peptic ulcer. The initial lesion or acute ulcer occurs during adrenal insufficiency (hypocorticism) as a result of a stressful situation. This is followed by hyperactivity of the adrenal glands (hypercorticism) either endogenous or exogenous. The anti-inflammatory action and the hypersecretion of acid and pepsin in the stomach, caused by hypercorticism, may disturb the balance between tissue destruction and tissue repair, and may cause the acute ulcer to become deeper, leading to hemorrhage or perforation, or healing may be retarded, thus beginning the chronic stage of a peptic ulcer.

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NEEDLE BIOPSY OF THE LIVER IN MALIGNANT HEPATIC DISEASE

A Safe, Useful, Diagnostic Procedure

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Fisher and Faloon[1], in September, 1958, reported that five patients died after needle biopsy of the liver performed in a series of 341 patients. Four of the patients were in a group of 33 patients with metastatic malignant disease—a mortality of 12 per cent. They suggested that, "Needle biopsy of the liver in the presence of suspected malignant disease is hazardous and surgical biopsy under local anesthesia may be a preferable procedure in this situation."

The report of Fisher and Faloon[1] is at variance with the findings of other investigators (see Comment), and also with our own experience. We therefore are reporting the results of our studies on needle biopsy of the liver in hepatic malignant disease.

Material and Methods

The complications of needle biopsy of the liver from 1946 to 1953 were previously reviewed[2-4]. A review of the records of patients who underwent closed needle biopsy of the liver in the period of January, 1953, to January, 1958, revealed that 112 patients had proved hepatic malignant disease. Our indications for needle biopsy of the liver have been: 1. hepatomegaly, 2. suspected primary or metastatic malignant disease, 3. suspected granuloma, 4. hepatic dysfunction and/or jaundice in which the diagnosis was not clearly indicated by clinical and laboratory findings.

A suspicion of hepatic neoplasm was the indication for biopsy in all but two of the 112 patients. The two in whom malignant disease was not suspected underwent needle biopsy to confirm the diagnosis of cirrhosis, and to determine the extent of hepatic damage histologically; each was discovered to have an unsuspected hepatoma. On physical examination, a large nodular liver evoked the suspicion of hepatic malignancy in the other patients. In addition, 29 patients had survived for a period of 2½ to 10 years after resections of malignant lesions

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of the colon, stomach, breast, thyroid, or skin. An additional 21 patients had roentgen evidence of carcinoma in the gastrointestinal tract, in the skeletal system, or in the lungs.

The contraindications to needle biopsy to which we attempted to adhere were: 1. abnormal prothrombin time; 2. abnormal tendency to bleed, as evidenced either by a low platelet count or by clinical evidence such as ecchymoses, petechiae, purpura; 3. infection either with suspected hepatic abscess or with peritonitis; 4. ascites—only relative, since biopsy was frequently performed after ascitic fluid was removed by paracentesis; 5. an uncooperative patient who could not follow directions and hold his breath.

Blind biopsies of the liver were performed to establish a tissue diagnosis and to save the patient the expense and the discomfort of an exploratory lapa-

TABLE I

COMPARISON OF MORTALITY AND MORBIDITY IN NEEDLE BIOPSY IN MALIGNANT DISEASE OF THE LIVER IN TWO SERIES OF PATIENTS

Status	Number of patients in whom malignant diesase was diagnosed by needle biopsy	
	1946-1953 (previous series)	1953-1958
Total	100	108
Mortality	1	1
Morbidity	6	11
Bleeding	2	2
Pneumothorax	0	1
Pain	4	8

rotomy. All biopsies were done with the Vim-Silverman needle. The subcostal approach was used in patients with hepatomegaly (most of the patients), and the thoracic approach in those without hepatomegaly. The standard technic of biopsy was used, as described by Brown[3], and as visualized in a movie by Clark and Brown[4].

RESULTS

The mortality and morbidity of needle biopsy of the liver in the presence of malignant neoplasm are presented in Table I. The only fatality that could possibly be attributed to the biopsy in the group previously reviewed (1946-1953) occurred in a patient who was terminally ill with Hodgkin's disease, who had a low platelet count at the time of biopsy, and in whom hemorrhage developed after the biopsy. Biopsy was contraindicated because of the low platelet count and the tendency to bleed.

In the 112 cases in the recent series, there were four major and eight minor complications. The minor complications consisted only of pain at the site of biopsy, or abdominal distress for several hours after the biopsy.

The patient who died was a 68-year old man who had had severe weight-loss, anorexia, and cachexia; the liver was hard and nodular, 10 cm. below the right costal margin. The prothrombin time initially was 29 seconds, and after Mephyton® was 20 seconds. Immediately after the biopsy this patient had abdominal pain associated with an increase in pulse rate and a fall in blood pressure. Despite the administration of two units of blood, he failed to respond. Laparotomy was performed six hours after the biopsy and two small lacerations of the liver were sutured. The blood pressure and pulse were restored to normal, and the hemoglobin remained at 10 gm. per 100 ml.; nonetheless the patient

TABLE II

Diagnoses of Hepatic Neoplasm Made by Needle Biopsy (1953-1959)

Diagnosis	Number of Patients
Adenocarcinoma	55
Undifferentiated carcinoma	36
Hepatoma	7
Sarcoma	6
Melanoma	3
Lymphoma	3
Malignant carcinoid	1
Embryonal carcinoma of testis	1
Total	112

died on the sixth postoperative day. In this patient, the bleeding after biopsy was controlled by transfusion and operation, but apparently the trauma was excessive. Although death was soon to be expected in this patient who had terminal cancer, it is likely that the needle biopsy of the liver and the subsequent laparotomy hastened it. In this patient, just as in the patient in the previous series who died, the prolonged prothrombin time actually contraindicated biopsy. The two fatalities occurred in patients in whom the contraindications to biopsy were not strictly followed.

Two other patients showed evidence of intraabdominal bleeding after biopsy. In one patient right upper quadrant distress developed associated with a decrease in blood pressure and in blood hemoglobin concentration. A transfusion of one unit of blood, however, stabilized the blood pressure and hemoglobin, and the patient was discharged from the hospital four days after the biopsy. In one patient with an unsuspected hepatoma, hypotension developed

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after biopsy, and 5 units of blood were necessary to stabilize the blood pressure. He was discharged on the tenth day after biopsy.

In one patient, in whom the transthoracic approach was used, a tension pneumothorax developed, along with chest pain and dyspnea. After one aspiration of the air, the patient improved. This patient had an unsuspected hepatoma, as well as postnecrotic cirrhosis. She survived three and one-half years after the original tissue diagnosis of hepatoma was made.

Six patients died of the primary disease within 30 days of the biopsy. There was no evidence that these deaths were attributable to complications of the needle biopsies.

The diagnoses established by needle biopsy in the 112 patients are listed in Table II. One may be suspicious of hepatic malignant disease in a patient who has or has had malignant disease elsewhere and who is found to have a large, nodular liver. One may also have a high index of suspicion of hepatoma in a cirrhotic patient whose liver suddenly enlarges and whose clinical status and liver function tests suddenly deteriorate. Although one may be suspicious of hepatic malignancy, a definitive diagnosis can only be made by biopsy. We believe that a tissue diagnosis should be made for every patient in whom hepatic malignant disease is suspected.

Comment

Malignant disease of the liver was diagnosed by blind needle biopsy in 208 patients during 1946 to 1958. There were two fatalities after biopsy, in each of whom biopsy was actually contraindicated because of a tendency to bleed. Our findings, in contrast to those of Fisher and Faloon[1], suggested that needle biopsy of the liver in suspected hepatic malignant disease is a safe and useful diagnostic procedure. The needle biopsy of the liver resulted in a positive tissue diagnosis in our 208 patients and precluded the morbidity and mortality that are likely to occur in these poor-risk terminally diseased patients as a result of exploratory laparotomy. There appears to be no greater risk to needle biopsy of the liver because of the presence of hepatic malignant disease.

Other studies also indicate the relative safety of needle biopsy of the liver, whether malignant disease is present or absent, in contrast to the report of Fisher and Faloon[1]. Zamcheck and Klausenstock[5] extensively reviewed the literature in 1953, and found 34 fatalities following 20,016 needle biopsies, a mortality of 0.17 per cent. They stated: "There is abundant evidence that the frequency of serious complications, including death, is high in inexperienced hands."

Parets[6] reported no fatalities in biopsies on 113 patients with hepatic malignant disease. It was his conclusion that no greater risk existed in the use of needle biopsy in the presence of hepatic metastasis than existed in the presence of other accepted indications for biopsy. Nugent[7] states that the detec-

tion of otherwise unsuspected neoplasm is a particularly rewarding aspect of needle biopsy of the liver, and invariably eliminates an unnecessary surgical procedure.

Our findings are in agreement with those of Zamcheck and Klausenstock[5], Parets[6], and Nugent[7]. Needle biopsy of the liver in suspected hepatic malignant disease is a relatively safe procedure, and may result in a tissue diagnosis without subjecting the patient to the statistically higher morbidity and mortality associated with laparotomy in these patients, many of whom are terminally ill with metastatic cancer.

Summary

Of 100 patients who underwent needle biopsies of the liver during 1946 to 1953, in whom malignant neoplasm was proved, there was one fatality. In 112 similar patients who underwent biopsy of the liver, during 1953 to 1958, there also was one fatality. Other complications following biopsy were minimal and did not require surgery; they responded to transfusions and other medical treatment. Six additional patients died within 30 days of the biopsy, because of the primary disease and not because of the biopsy.

A high index of suspicion of hepatic malignant disease, primary or secondary, is one of the chief indications for needle biopsy of the liver. Such a biopsy has been a relatively safe procedure, and is preferable to the greater risk of laparotomy.

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EXPERIMENTAL AND CLINICAL CONSIDERATIONS ON HESPERIDIN-ASCORBIC ACID IN UPPER GASTROINTESTINAL BLEEDING*

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Introduction

Reported observations suggest that Vitamin C and bioflavonoids are beneficial in the treatment of peptic ulcer[1-4]. The Vitamin C level in the blood and gastric juice of ulcer patients has been found to be 56 and 59 per cent lower, respectively, than in normal individuals[5]. This depletion of Vitamin C may be secondary to diet, stress and possibly other factors. These observations, the vascular effect of Vitamin C and its role in the healing of tissue lesions, and the demonstrated inhibitory effect of the bioflavonoids in histamine release[6], prompted us to study the effects of a combination of hesperidin (a flavonone glycoside) and Vitamin C on gastric hemorrhage induced in healed ulcer patients by administration of histamine-insulin; a phenomenon described by Bodi et al[7]. Clinical evaluation of this combination of hesperidin-ascorbic acid was also made in selected cases of subclinical and massive bleeding in peptic ulcer patients.

Experimental Considerations

In the experimental part of our study, five ulcer patients volunteered for histamine-insulin stimulation and the hesperidin-ascorbic acid treatment. Technics for the experimental production of gastric hemorrhage have been reported elsewhere[7]. Gastric bleeding was established by serial aspiration of gastric content. The diagnosis and the duration of therapy is summarized in Table I.

After the initially induced hemorrhage with histamine-insulin stimulation, the patients were treated with a combination of hesperidin 100 mg. ascorbic acid 100 mg. in each capsule‡ (two capsules three times daily for one week). No other medication was given during this period; however, all of the patients adhered to strict ulcer diet. After 7 days of hesperidin-ascorbic acid treatment in 4 patients and 14 days in the fifth patient of this series, they were again

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‡Supplied by the National Drug Company, Philadelphia, Pa.

subjected to histamine-insulin stimulation. The degree of hemorrhage was compared with that of the pretreatment phase. Gastric acidity, pH, pepsin, muco-protein, mucoproteose and viscosity were estimated in the gastric juice as quoted by Bodi et al[7].

Clinical Considerations

Twelve ulcer patients with established subclinical or gross bleeding from the upper gastric tract were selected for the evaluation of the clinical effect of hesperidin-ascorbic acid. One case with upper gastric bleeding suspected of ulcer was finally diagnosed as bleeding from esophageal varices. Evidence of bleeding was established by observation of gross blood in the stools, stool guaiac test, and occasionally by the gastric braid test.

The patients were maintained on standard ulcer therapy including antacids and ulcer diets, in addition to the hesperidin-ascorbic acid combination. The

TABLE I

No.	Name	Age	Sex	Diagnosis	Duration of ascorbic acid-hesperidin therapy.* (Days)
1	J.P.	33	M	Duodenal ulcer	7
2	W.L.	45	M	Duodenal ulcer	7
3	J.C.	55	M	Duodenal ulcer	14
4	J.B.	25	M	Duodenal ulcer	7
5	M.R.	56	M	Gastric ulcer	7

*Histamine-insulin stimulation before and on completion of therapy.

patient's clinical response, manifested by cessation of hemorrhage, was checked by periodic stool guaiac tests. X-ray examinations were made before treatment to verify the clinical diagnosis and to establish our clinical impressions of the treatment.

Results in Experimental Group

Table II shows the effect of hesperidin-ascorbic acid on repeated histamin-insulin stimulation. In one patient (Case 2), almost total absence of blood was observed. In another patient (Case 1), there was considerably less bleeding as compared to prehesperidin-ascorbic acid treatment. In Case 4, a slight reduction was found in the 60-minute posthistamine-insulin specimen. Two patients showed no change in the amount of blood in the gastric aspirations after one week of hesperidin-ascorbic acid treatment. (One of these patients had a large ulcer crater prior to the initial stimulation which was markedly reduced following the one week treatment with the hesperidin-ascorbic acid combination.)

The pH, acidity and pepsin values showed close agreement in both the pre- and posttreatment experiments as shown in Tables III, IV, and V.

The mucoprotein values showed a considerable rise in the 40-minute post-histamine-insulin specimens in 4 patients.

The mucoproteose results were variable with no consistent values.

Viscosities were measured in only two cases and were not significantly different.

Clinical Results

Eleven peptic ulcer patients and one patient bleeding from esophageal varices were treated with a regimen prescribed for bleeding ulcers plus

TABLE II

Effect of Hesperidin-C Therapy on Blood Concentration in Gastric Juice after Histamine-Insulin Stimulation

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	0*	0	1	0	5	0	0	0	0	1
30′ after histamine	8	0	8	1	5	0	0	5	0	1
20′ after insulin	8	5	6	0	5	5	5	5	5	6
40′ after insulin	8	5	5	0	5	6	5	5	6	5
60′ after insulin	8	1	8	1	8	8	7	5	5	5

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.
*Numbers 1 through 8 refer to the blood concentration in the specimen as compared to standards defined by Bodi et al[7].

hesperidin-ascorbic acid, either in capsule containing 100 mg. each of hesperidin and ascorbic acid or tablets containing 200 mg. of each administered two to three times daily. In eleven instances, the stool guaiac test changed to negative within two or three days. In one patient the stool guaiac test was positive for two weeks during treatment.

Case Reports

Six cases are presented to show the clinical course under the ulcer treatment supplemented with a combination of hesperidin-ascorbic acid.

TABLE III

FREE AND TOTAL ACID

Time	Case Number																			
	1				2				3				4				5			
	FA		TA		FA		TA		FA		TA		FA		TA		FA		TA	
	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P
Fasting	50	32	80	55	59	50	86	66	54	52	85	74	15	7	34	31	23	13	54	31
30′ after histamine	101	97	130	115	73	85	111	115	90	94	120	115	56	63	81	90	85	60	115	73
20′ after insulin	119	115	148	142	81	62	122	84	92	80	117	97	31	39	54	51	78	53	98	70
40′ after insulin	107	117	137	140	122	125	156	154	104	82	136	96	95	103	125	126	30	75	53	98
60′ after insulin	108	117	152	140	120	107	152	137	114	99	146	124	92	91	119	116	25	75	50	94

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.
FA = Free Acid; TA = Total Acid.

Case 1:—(D5902) This 34-year old white male had a history of intermittent melena for four years and had been hospitalized on one occasion in July, 1958. The diagnosis was an active duodenal ulcer and treatment consisted of diet, anticholinergic and antacid medication. In September, 1958, following recurrence of bleeding, this therapy was supplemented with hesperidin (200 mg.)—ascorbic acid (200-mg.) in a compressed tablet—one tablet twice daily, after meals. After one month of treatment, both the stool guaiac test and the gastric braid test had changed from positive to negative. Guaiac tests repeated for 3 weeks remained negative. Treatment was continued with one hesperidin-ascorbic acid tablet daily. On 10 March 1959, the hemoglobin had risen from 89 to 96 per cent; the stool guaiac test was still negative and the x-rays showed definite ulcer healing.

TABLE IV

pH Determinations

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	1.1	1.3	1.4	1.4	1.4	1.2	2.5	2.9	1.9	2.0
30′ after histamine	1.0	0.7	1.3	1.2	1.2	1.0	1.4	1.3	1.0	1.2
20′ after insulin	0.9	0.9	0.7	1.3	1.2	1.1	1.6	1.7	1.1	1.4
40′ after insulin	1.0	0.9	0.9	0.9	1.1	1.1	1.0	1.1	1.7	1.1
60′ after insulin	1.0	0.9	0.6	1.0	1.1	1.0	1.0	—	1.3	1.2

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.

Comment:—The hesperidin-ascorbic acid combination apparently prevented for three months the recurrence of further bleeding episodes in this patient.

Case 2:—(D4953) This 48-year old white woman was admitted with a history of acute hematemesis and melena in October, 1956. She was placed on a standard diet, antacid therapy, and three hesperidin-ascorbic acid capsules daily. After two weeks, the patient was discharged asymptomatic. On 24 January 1957, a duodenal ulcer was revealed by x-ray studies. The patient was then placed on a modified ulcer regimen and one hesperidin-ascorbic acid capsule daily. During a three-month period, the hemoglobin rose from 77 to 84 per cent and repeated guaiac tests were negative. Hesperidin-ascorbic acid supplemented by an antacid and an anticholinergic drug was continued for the next two years. The guaiac tests remained negative and there was no evidence of bleeding during

this period. The patient was re-checked on 18 March 1959; the hemoglobin was 84 per cent, there was no evidence of bleeding, the stool guaiac test was negative and the patient had no complaints.

Comment:—It is difficult to conclude that hesperidin-ascorbic acid therapy in this patient protected against possible hemorrhagic episodes. It is of interest that this patient showed no clinical evidence of bleeding while taking hesperidin-ascorbic acid.

Case 3:—(D6118) This 47-year old white male had a history of duodenal ulcer for five years and had been hospitalized in December, 1958 with massive upper gastrointestinal hemorrhage. In January, 1959, he had occult blood loss in the stool and was started on a therapy of a modified Meulengracht diet, a

TABLE V

PEPSIN VALUES

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	0.194	0.152	0.154	0.142	0.149	0.179	0.135	0.141	0.174	0.139
30′ after histamine	0.261	0.240	0.205	0.202	0.179	0.225	0.122	0.193	0.034	0.199
20′ after insulin	0.223	0.229	0.145	0.171	0.142	0.178	0.113	0.295	0.219	0.160
40′ after insulin	0.280	0.280	0.380	0.367	0.268	0.231	0.239	0.374	0.215	0.277
60′ after insulin	0.235	0.276	0.398	0.349	0.224	0.146	0.224	—	0.277	0.238

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.

liquid antacid preparation and hesperidin-ascorbic acid tablets. After four days, the guaiac test for occult blood was negative. The patient was continued on antacid therapy, a full Meulengracht diet and one capsule of hesperidin-ascorbic acid daily for two months. His hemoglobin rose from 76 to 94 per cent, and the guaiac test was still negative. The medication was discontinued and the patient was advised to avoid smoking and emotional stress.

Comment:—It is probable that hesperidin-ascorbic acid had a positive clinical effect on the intermittent bleeding in this patient. There were no further episodes of bleeding.

Case 4:—(D3189) In the history of this 43-year old white male there was evidence of recurrent melena since 1951. The diagnosis was gastric ulcer and

standard diet and antacid therapy were prescribed. In May of 1955, this patient was hospitalized because of severe epigastric distress following an emotional upset, melena, and placed on two capsules of hesperidin-ascorbic acid three times daily. In three days, the guaiac test changed from four plus to two plus and after seven days it was negative for occult blood. X-rays revealed a duodenal ulcer. The patient was seen intermittently between 1955 and 1959 during which time there was no evidence of occult blood in the stools. Then after taking a "super-aspirin" with anticholinergic and tranquilizer, the patient again reported a tarry stool. The medication was a combination of prednisolone, aspirin, and a "buffering antacid"; the ulcer appeared to have been reactivated, secondary to "buffered" steroid therapy. The patient was taken off all medication and placed on modified ulcer diet and one hesperidin-ascorbic acid tablet four times

TABLE VI

MUCOPROTEIN VALUES

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	79.7	41.9	32.5	56.6	—	90.1	57.6	63.9	0.0	38.7
30′ after histamine	123.7	88.0	32.5	80.7	84.9	31.4	40.8	188.8	0.0	149.9
20′ after insulin	74.4	75.5	32.5	42.9	72.3	58.7	35.6	217.1	0.0	24.1
40′ after insulin	184.6	123.7	206.6	284.2	204.5	221.3	182.5	368.1	0.0	254.8
60′ after insulin	153.1	115.3	189.8	204.5	—	116.4	148.9	—	—	12.6

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.

daily after meals. Four days later, the stool guaiac test was negative. One capsule of hesperidin-ascorbic acid daily was prescribed and an analgesic buffered with an antacid was suggested for vague back pains.

Comment:—With hesperidin-ascorbic acid therapy, there was a rapid disappearance of blood from the stools of this patient, and no further bleeding from the upper gastrointestinal tract was noted.

Case 5:—(D6210) This 51-year old white male had a history of epigastric pains and repeated bouts of hematemesis for 12 years prior to a subtotal gastrectomy in October, 1954. Pathological studies of removed tissue revealed some evidence of active ulcer. On 16 February 1959, he was being treated for melena and all conservative measures had been tried without effect. A diet of milk (3 oz.) with a teaspoonful of sugar, sipped every 2-3 hours was prescribed and

the patient was also placed on two hesperidin-ascorbic acid tablets four times daily. Within 36 hours, the stool became light brown, still positive for occult blood. Within 96 hours, on the above regimen, the stool was negative for occult blood. A soft bland diet was instituted, 2 mg. Benat with B_{12} were given twice weekly, and hesperidin-ascorbic acid dose was reduced to 4 tablets daily. Nine days later, x-rays were taken and showed esophageal varices, no marginal ulcer. The patient was advised to refrain from tobacco, alcohol and highly seasoned foods. The patient was discharged on a modified bland diet, and one hesperidin-ascorbic acid tablet daily for prophylaxis.

Comment:—Refractory esophageal bleeding was apparently arrested with the ulcer regimen, hesperidin-ascorbic acid in large doses, and bed rest.

TABLE VII

MUCOPROTEOSE

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	131.2	11.8	1.8	41.6	—	34.1	47.6	27.7	161.0	31.7
30′ after histamine	41.6	43.6	0.0	31.0	37.6	—	15.6	65.5	226.7	75.4
20′ after insulin	15.7	25.7	7.8	105.3	43.6	312.2	39.6	69.5	190.6	190.6
40′ after insulin	103.3	51.6	33.6	43.6	49.6	—	43.6	65.5	340.1	184.9
60′ after insulin	5.8	31.7	31.7	41.6	—	—	39.6	—	—	73.4

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.

Case 6:—(D4463) This 63-year old white male had a history of melena and hematemesis and had been advised to have a subtotal gastric resection, but patient refused surgical intervention. On 26 April 1956, the patient had severe emotional upset, melena and was placed on Meulengracht diet supplemented with two hesperidin-ascorbic acid capsules three times daily for ten days, and I. M. injections of 500 mcg. Vitamin B_{12} twice weekly. By the fifth day, the stool guaiac test had changed from 4 plus to 1 plus for blood. From the seventh day on, the stool guaiac test was negative. The patient was not seen again until 13 March 1957 when he had a tarry stool which was 4 plus guaiac. During the past several months the patient had "gone off" his medication and diet, resumed smoking and was under severe emotional stress. Hesperidin-ascorbic acid supplement was again given (2 capsules three times daily). On 18 March 1957, stool guaiac test was negative. Patient was continued on hesperidin-ascorbic acid supplement (one capsule three times daily) for 6 weeks. Since the patient was

indifferent in following his diet and taking his medication, he was advised to come in regularly for check-ups. From August, 1958 to March, 1959, patient was given a strict diet, supplemented with hesperidin-ascorbic acid. He followed this regimen sporadically, however, and several guaiac positive tests were reported. Negative results were obtained when hesperidin-ascorbic acid therapy was resumed.

Comment:—A case in which melena appeared to be controlled so long as the patient continued taking hesperidin-ascorbic acid regularly.

Comment

In previous experiments we produced a high incidence of minor, but significant, gastric hemorrhages following histamine-insulin stimulation in duodenal

TABLE VIII

Viscosity

Time	Case Number									
	1		2		3		4		5	
	O	P	O	P	O	P	O	P	O	P
Fasting	—	—	—	—	—	—	1.194	1.322	1.427	1.194
30′ after histamine	—	—	—	—	—	—	1.179	1.097	1.287	1.945
20′ after insulin	—	—	—	—	—	—	1.154	1.174	1.487	1.391
40′ after insulin	—	—	—	—	—	—	1.105	1.112	1.679	1.499
60′ after insulin	—	—	—	—	—	—	1.173	—	1.700	1.458

O = Pretreatment; P = Posttreatment with hesperidin-ascorbic acid.

and gastric ulcer patients[7]. This was in sharp contrast to individuals without gastrointestinal complaints, and negative upper gastrointestinal series. A similar phenomenon was occasionally noted after repeated injections of histamine[7]. The reaction, however, was sporadic compared to successive stimulation by histamine and insulin.

Histamine and insulin stimulation was proposed as a "comprehensive test of gastric secretory function"[8]. Central vagal action subsequent to insulin hypoglycemia stimulates the nonparietal components of gastric secretion, viz., pepsin and mucous substances. The response is probably mediated directly by discharge of acetylcholine at the vagal endings of the stomach. Large doses of acetylcholine when used experimentally caused vasodilation and bleeding from the pyloric

mucosa.[9,10]. In animal experiments, mucosal erosions and hemorrhage situated mainly in the pyloric portion were produced by large doses of insulin[11]. Similar "insulin gastritis" may explain the hemorrhagic phenomenon of our ulcer patients.

There are probably a series of events responsible for vascular stress. Vasodilation by histamine and acetylcholine in the mucosa, stasis, edema, hyperacidity, and probably hypermotility, presumably in the synergistic series, act to cause capillary injury, interstitial hemorrhage, necrosis and mucosal erosion.

Alcoholic excesses and overloading of the stomach are clinically correlated to the precipitation of hemorrhages in many instances[12]. Histamine release may be a factor in the mechanism of postalcohol stimulation of gastric secretion and perhaps hemorrhage[13].

Trauma did not seem to be a factor in producing hemorrhage in the course of our experiments. The passage of the Levin tube did not cause bleeding in our normal controls. The presence of occult blood was minimized through careful technic. The initial aspirations from ulcer patients were clear and rarely positive for occult blood. The appearance of gross blood, however, almost without exception, paralleled the peak of the insulin effect. It is possible that the response of the ulcer patients to the drugs was different due to the increased vasodilation and mucosal friability. Under such circumstances, hypermotility and perhaps the presence of antral gastritis would predispose the tissues to fragility, erosion and hemorrhage.

Vitamin C is required, among others, for capillary integrity. Hesperidin was found to reduce histamine toxicity in normal animals[14], and it has been postulated that hesperidin methylchalcone may inhibit release of histamine from blood cells[15]. Any beneficial role may be theoretically explained on these grounds in the postinsulin-histamine hemorrhage. The bleeding ulcer patient probably is deficient in Vitamin C due to prolonged anorexia with the preceding deterioration and perhaps as a result of too rigid ulcer dieting; and a diet deficient in fresh fruits. This is supported by the observations of Freeman et al[5]. Our clinical observations seemed to support this concept by the good response of patients to the hesperidin-ascorbic acid combination when added to the standard ulcer management. Hesperidin combined with ascorbic acid is an established effective agent in correcting capillary defects in the presence of certain disease states[16].

When we consider that the acute gastric hemorrhage in the experimental patient was produced by powerful stimulation of the administered histamine-insulin, and that hesperidin-ascorbic acid does not seem to have a corresponding acute protective effect, it may be said that perhaps a longer period of treatment is needed to meet the hemorrhage producing challenge of histamine-insulin. This is suggested by the results obtained in three of the five patients tested. In our clinical cases, the results were suggestive of good response, although a

much larger series of patients and controls with placebo must be included to draw a definite conclusion.

Conclusions

In our experimental study, hesperidin-ascorbic acid therapy reduced the amount of posthistamine-insulin gastric hemorrhage in three out of five patients with peptic ulcer. Eleven patients with peptic ulcer, followed for gastroduodenal hemorrhage from 2 months to several years, and one patient bleeding from esophageal varices, seemed to be benefited by the standard ulcer therapy supplemented with hesperidin-ascorbic acid.

This combination may be a useful adjunct in the therapy of bleeding ulcer and warrants further clinical evaluation.

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Addendum

Since completion of this report, Morris [Postgrad. Med. **27**:207, (Feb.) 1960] reported two cases of hemorrhagic gastritis caused by a deficiency of Vitamin C. Administration of large doses of Vitamin C and citrus juice prevented recurrences of gastric bleeding.

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EVALUATION OF AMBUTONIUM BROMIDE IN THE MANAGEMENT OF GASTROINTESTINAL DISEASE

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It is well known that medical treatment alone cannot cure patients who have gastrointestinal diseases such as duodenitis, gastric ulcer, or colitis; it can only create the best possible conditions for the process of healing, and thereby make healing easier and more rapid. Relaxation and rest, both physical and mental, are of the utmost importance in creating the required conditions, but even these are often inadequate without proper medication and diet.

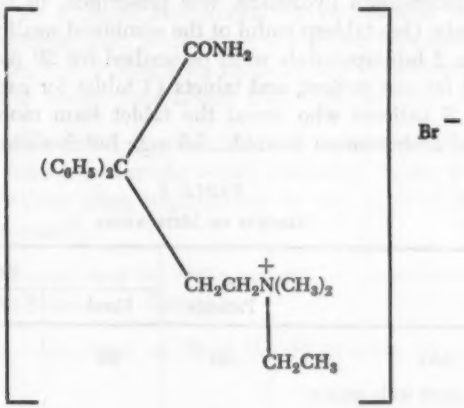
Recently, there has been increasing dissatisfaction with anticholinergic drugs alone in the treatment of patients who have peptic ulcers[1-3]. Atropine and its derivatives, the most widely used of all the anticholinergic compounds, are unpredictable in their effect on the stomach, and do not produce, consistently, the desired degree of secretory inhibition without side-effects such as xerostomia, difficulty in swallowing, tachycardia, mydriasis, urinary retention, constipation, nausea and vomiting, and drowsiness[4]. The ideal antisecretory agent should selectively inhibit the vagal mechanism without appreciable ganglionic blockade or curariform activity, it should be safe and palatable, and have the ability to suppress acid secretion completely for long periods of time after oral administration without the development of drug tolerance or disturbing side-effects[5]. Although many of the newer antisecretory drugs appear to be more effective, they still do not produce the desired degree of secretory inhibition without producing side-effects, and are far less effective when given orally than when administered parenterally[6].

The purpose of the present study was to evaluate the effectiveness of the anticholinergic, ambutonium bromide, when given in combination with aluminum hydroxide gel, magnesium hydroxide gel and butabarbital, in alleviating ulcer-like symptoms in 54 patients, 25 of whom had previously received therapy in the form of antispasmodics, sedatives and tranquilizers, and antacids, or combinations thereof. Although it usually is recommended that such ingredients be given separately, the combined medication* has been found to be much more convenient for use by the patient, the physician, and the nursing personnel.

The sedative properties of butabarbital[4] and the efficacy of aluminum hydroxide gel[7-10] and its combination with magnesium hydroxide[11,12] in the control of gastric hyperacidity and the relief of pain and hyperacidity in peptic ulcer are well established. They do not require further explanation other than to mention the fact that the addition of magnesium hydroxide to the combination provides a constipation-inhibiting effect without producing diarrhea.

* Aludrox® SA, Wyeth Laboratories

Ambutonium bromide [(3-carbamoyl-3, 3-diphenylpropyl) ethyldimethylammonium bromide] is a new anticholinergic agent which has the following structural formula:



Animal studies have shown ambutonium bromide to be effective in reducing secretory volume, small bowel and colonic motility, and in blocking the spasmogenic effects of acetylcholine, arecoline, and pilocarpine[13].

The pharmacologic properties of ambutonium bromide in human subjects were first studied by Judge, Bolt, Hirschowitz, and Pollard[14] who found that from 10 to 25 mg. of ambutonium bromide, administered orally, significantly reduced gastric acidity and secretory volume without significant side-effects in normal male subjects. Also, that ambutonium bromide, 12.5 mg. administered orally, was superior to atropine sulfate, 0.6 mg. administered orally, in its effect on gastric secretion, and that from 12.5 to 25 mg. of ambutonium bromide, administered orally, was superior to atropine sulfate 0.6 to 1.0 mg., administered orally, in its effect on gastric motility. No tolerance to the secretory or motility inhibiting effects of ambutonium bromide developed after administration of 12.5 mg. four times daily for a period of 7 days. Clinical studies were first carried out by Bolt, who evaluated the side-effects, toxicity, and therapeutic value of ambutonium bromide. A dose of 15 to 20 mg. was prescribed four times daily for a period of from 1 to 3 months for 124 patients who had duodenal ulcers. Toxicity was not seen in his patients.

Procedure

Fifty-four unselected, private patients, 29 women and 25 men from 19 to 63 years of age, were included in this study. The average age of the patients was 44.7 years. A thorough history was taken and a complete physical examination was made during the initial visit of each patient. The diagnoses made for

these patients were confirmed by roentgenologic examination, and are presented in Table I.

The combination of aluminum hydroxide gel, butabarbital, ambutonium bromide, and magnesium hydroxide, was prescribed, in liquid or tablet form, for all 54 patients. One tablespoonful of the combined medication was prescribed for 21 patients; 2 tablespoonfuls were prescribed for 26 patients; 1 teaspoonful was prescribed for one patient, and tablets (1 tablet for each teaspoonful) were prescribed for 5 patients who found the tablet form more acceptable. (Each tablet contained ambutonium bromide, 2.5 mg.; butabarbital, 8.0 mg.; aluminum

TABLE I

RESULTS OF MEDICATION

Diagnosis	No. of Patients	Results		
		Good	Fair	Poor
Duodenal ulcer	30	24	4	2
Duodenal ulcer with spastic colitis	1		1	
Duodenal ulcer with gastric diverticulum	1	1		
Duodenitis	14	12	1	1
Duodenitis with spastic colon	1		1	
Colitis:				
ulcerative	1	1		
spastic	1			1
chronic ulcerative	1			1
chronic ulcerative with spastic colon	1	1		
Gastrointestinal anxiety state	2			2
Postgastrectomy syndrome	1		1	
Totals	54	39	8	7

hydroxide equivalent to 1 teaspoonful of aluminum hydroxide gel; and magnesium hydroxide equivalent to one-quarter teaspoonful of milk of magnesia.) The aforementioned doses of the medication were taken 2 hours after eating and, in some instances, at bedtime. The remaining patient in this study took 2 tablespoonfuls of the combined medication whenever necessary.

In addition to the combined medication, the usual bland ulcer diet was prescribed, and the patients were directed to restrict their physical activity.

The patients were seen in the office once each week to once each month, depending on the progression or regression of symptoms, and interviews and

examinations were carried out at that time. Evaluation of the medication was made by classification of the results as good, fair, or poor. The results were considered good when there was a remission of symptoms by the end of the first week and continued remission on follow-up in the office, with examination and discussion every week for a period of 6 weeks. The results also were considered good when patients reported that, when there was an exacerbation of symptoms, they disappeared within 1 to 2 days after medication was reinstituted. This was true for every patient in whom good results had been obtained initially.

Results were considered fair in those patients in whom the symptoms persisted for a period of from 4 to 6 weeks before remission. Again, when symptoms recurred, the exacerbations often required up to one week of therapy before symptoms again disappeared.

Results were considered poor for those patients in whom there was no relief of symptoms after 4 to 6 weeks of therapy.

Follow-up studies were done on 36 of the 54 patients for a period of approximately one year.

Results

Of the 54 patients, 47 responded to medication; 7 did not. The results were good in 39 patients (72 per cent), fair in 8 (15 per cent), and poor in 7 (13 per cent). The results obtained by individual groups are presented in Table I. The best results were seen in those patients who had upper gastrointestinal diseases; the poorest by those patients who had diseases of the large intestine, and those who did not have any organic disease. The duration of medication varied from 1 week to 6 months. The average duration of medication was one month.

Side-effects were mild and usually abated on continuation of the medication in the same dosage or on reduction of the dosage. In not one instance did the presence of side-effects necessitate the discontinuation of the medication. Side-effects observed were sleepiness (6 patients), constipation (5 patients), nausea (2 patients), dry mouth (3 patients), and blurred vision (1 patient).

Within a period of from 6 to 8 weeks after institution of therapy, follow-up roentgenologic examinations were made in 8 of the patients who had duodenal ulcers. The roentgenograms showed either disappearance or virtual disappearance of the ulcer in each instance.

The average patient who was on this therapy continued the daily routine of work or housework and, therefore, did not have the benefits of rest and freedom from mental strain during the entire course of treatment. The absence of symptoms was the basic criterion for determining whether or not the patient had obtained a good response.

Although the specific action of each of the individual ingredients of the medication prescribed is well known, the combination was evaluated on its own merits rather than on the merits of the individual components. Even in hospital practice, the evaluation of particular components or particular therapy is very difficult because the average hospitalized patient has a moderate amount of bed rest, emotional problems are usually at a minimum because he is being cared for, and he is given a bland diet, sedatives, and antacids, as well as the anticholinergic medication. I believe that all these are important, and that when one medication can offer several therapeutic approaches simultaneously, it is certainly well adapted to ambulatory patients.

Conclusions

Of the 54 patients in the study, 47 responded to combined medication containing aluminum hydroxide gel, butabarbital, ambutonium bromide and magnesium hydroxide; diet and reassurance. The results were good in 72 per cent of the patients, fair in 15 per cent, and poor in 13 per cent. The side-effects were minimal and did not require discontinuance of the medication. The combination was especially useful in the treatment of patients who had upper gastrointestinal disease, especially duodenal ulcer, and was ideally suited for those patients who had to continue their daily routine of work.

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JAUNDICE IN A PATIENT RECEIVING ZOXAZOLAMINE (FLEXIN)

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The patient, a 63-year old male with gout, had been on Zoxazolamine (Flexin) 250 mg. twice a day for 12 days when he developed jaundice. A diagnosis of gout was first made about 1947. The chief symptom had been pain and swelling of the right big toe. He had acute attacks every six to 12 months with some residual pain between attacks. X-rays of both feet showed moderate osteoarthritic changes but no changes suggestive of gout. The uric acid varied from 4.5 to 6.0 mg. (normally 2-3.5 mg.). He had various treatments including Colchicine, Benamide and Butazoladine. ACTH gave the best relief of acute exacerbation. The last acute attack of gout came in November, 1958, with pain in the knees and foot. This time he responded well to ACTH and Meprolone #2 (Meprobamate 200 mg. and Prednisone 2 mg.) five a day. This was reduced to one in the morning and two at bedtime as a maintenance dose, as he continued to have minor pains in his knees and occasionally in his foot. In June, 1959, Zoxazolamine was tried for more complete relief. Zoxazolamine has been shown by Reed et al[1] to be a uricosuric agent in the relatively low doses of 250 mg. to 1 gm. a day, as compared to its muscle relaxant effects in doses of 2 to 6 gm. a day. He was given one tablet of Flexin 250 mg. twice a day. After about one week, he noticed he was not feeling well. He lost his appetite and felt weak. A few days later his urine turned dark so he discontinued medication. He refused hospitalization as he "did not feel that sick".

Examination showed him to be icteric, liver slightly tender, otherwise normal, with his usual blood pressure of 160/80 and a temperature of 98.0 degrees. The urine showed a trace of albumin, a trace of sugar, a 4+ bile and the microscopic was essentially normal. The other tests are summarized in Table I.

Treatment consisted of aspirin for pain, vitamins by mouth, and injections of B-complex and 40 c.c. ACTH jel I.M. twice a week for two weeks. By then he had made a good clinical recovery from his jaundice. His pains, however, recurred with typical swellings in his foot and pains in his knees and elbows. This was controlled by ACTH (Acthar jel) 40 units every two weeks and Meprolone #2 q. i. d.

Comment

It is impossible to prove an isolated case of jaundice is due to a particular drug. Hoffbauer et al[2] reported two cases of fatal necrosis in patients taking Zoxazolamine. These were cases of diffuse necrosis about which the pathologist

differed on etiology. Zimmerman[3] classifies Zoxazolamine among the hypersensitivity reactions. Zoxazolamine has not been shown to be a liver toxin. William Amols[4] reported a series of 28 cases receiving from two to six gm. of Zoxazolamine with "no deleterious effects noted in blood counts, urinalysis, or liver and kidney function tests". This case does not fit a toxic hepatitis but fits the type of cholangiolitic hepatitis found in drug sensitivity reaction. Shay and Siplet[5], in their study on the mechanism of chlorpromazine jaundice, showed a temporary rise in alkaline phosphatase, little or no reaction in the cephalin flocculation, and the SGOT only moderately elevated for a short while. The moderately elevated SGOT may be due to increased cell permeability rather than cell destruction. Kemp[6] has shown the same type of reaction with promazine. Others have shown similar intrahepatic obstructive jaundice with methyltestosterone, oraphenamine, thiouracil, estrogens, butazoladine, dinitophenol, para-aminosalicyclic acid and sulfonamides. Arias and Zamcheck[7] postulate that the mechanism may be faulty glucuronide conjugation rather than an allergic reaction.

TABLE I

Test	Date			
	24 Jun	8 Jul	30 Jul	25 Sept
Bilirubin (total)	7.2	1.8	1.5	0.9
Alkaline phosphatase	44.0	44.0	18.0	–
SGOT	51.0	–	–	–
Cephalin flocculation	4+	–	neg.	neg.
Uric acid	–	5.8	–	5.0
Cholesterol	–	–	154	–
Urinary bile	4+	neg.	neg.	neg.

In conclusion, the case reported fits the type of intrahepatic obstructive jaundice found in other cases due to drug sensitivity. Clinically the patient is not too sick, the positive physical findings are little except jaundice and, sometimes, liver enlargement and tenderness, the alkaline phosphatase is elevated early but falls rapidly, the SGOT is moderately elevated for a short while and the cephalin flocculation test is usually negative. In this case, the cephalin flocculation test was high on the first test and thereafter normal. The first may have been a false high test as it is unusual for a 4+ to clear as rapidly as this one did.

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PERIODIC PERITONITIS AND ACUTE APPENDICITIS

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Many victims of periodic peritonitis have had appendectomy, cholecystectomy, laparotomy, tonsillectomy and exodontia performed in the hope of relieving the symptoms, for diagnostic purpose, and because of mistaken diagnosis, only to have the episodes resume unchanged. Nevertheless serious abdominal emergencies may occur in such persons. Although episodes of acute pain, tenderness and rigidity in the right lower quadrant with vomiting, fever and leucocytosis have recurred regularly without consequences for years, the appendix on occasion may be obstructed, infected, suppurate and rupture. Because diagnosis is obscure at times, the advisability of prophylactic appendectomy must be considered in persons with periodic peritonitis. A case in point is reported on here.

Report of a Case

An Iranian Army officer, aged 26, had dysentery in 1955 that was followed by short uniform bouts of abdominal pain about once a month spaced by intervals of health for 4 years. Episodes ceased several times for 3 to 6 months, but each time resumed a monthly sequence. Pain in the epigastrium began abruptly usually early in the morning, spread to the rest of the abdomen and to both shoulders. It intensified for several hours, then abated with exacerbations for 48 hours. Constipation or diarrhea was noted.

He attended the Out-Patient Clinic in April, 1958, during a free interval. No abnormalities were found except roentgen evidence of a spastic duodenum. Without specific information of past events at that time, neurosis or duodenal ulcer was suspected.

He revisited the clinic on further occasions having had recurrent episodes. Yet the nature of the disorder was not apparent until suggested by an alert lay interpreter. He then came to our attention. An episode began on 27 December 1958, and the patient entered the hospital for study. He had a flushed face, injected conjunctivae, coated tongue, fever of 37.4 C and a pulse rate of 96. There was general abdominal tenderness and pain was referred to the right side of the chest and neck. The leucocytes numbered 12,500. Discomfort ended in 48 hours, as usual. On inquiry, incapacitating episodes dated by his army record had occurred on 25 July, 2 September, 1 October, 1 November, 1 and 27 December

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at respective intervals of 39, 29, 31, 30 and 26 days. Periodic peritonitis was diagnosed.

On 19 January 1959, 23 days after the prior episode, severe pain, this time in the right lower quadrant, wakened him at 4 A.M. On readmission to the hospital there were rigidity and guarding of muscles in that area, nausea, vomiting, fever of 37.4 C and 10,600 leucocytes. Because of the onset of pain in a different place after the shortest recorded interval, appendectomy was performed. The decision was made because of the possibility of acute suppurative appendicitis and for prophylactic reason. The patient was a soldier subject to duty in regions devoid of medical facilities.

At operation, visualized parts of the ileum, cecum and colon were normal and there was no free fluid. The distal two-thirds of the appendix were edematous, scarred and covered with a yellow exudate that extended into the mesenteric fat. The wall was 2 mm. thick, hemorrhagic and focally ulcerated. The lumen contained pus and colon bacilli. Histologically, there were acute inflammation, granulocytic infiltration and ulceration. The mucosa in some places was normal, in others it was ulcerated or infiltrated with neutrophils and erythrocytes. Phlegmonous infiltration and hemorrhage involved the corresponding parts of the submucosa, muscle layers and particularly the subserosa and serosa. Some segments of the appendix were fibrotic. Apparently, acute suppuration had occurred in an appendix previously involved in periodic peritonitis.

When the patient was last seen 2 years later, he had no further episodes. Short bouts of mild abdominal pain at undated intervals of 2 or 3 months occurred, but whether or not these were mild episodes of periodic peritonitis is uncertain.

Comment

There was no doubt as to the presence of acute appendicitis, impending rupture and its consequences. If spontaneous healing would have ensued as in prior episodes of periodic peritonitis cannot be said. The lesion was like that of the familiar kind of appendicitis induced by obstruction and infection involving the mucosa, and the purulent granulocytic process spreads outward. In contrast, the sterile, nonpurulent, lymphocytic appendiceal inflammation in an episode of periodic peritonitis is a part of a local or general peritoneal reaction. It begins in the serosa and spreads inward to the muscularis without affecting the mucosa. Scars and adhesions are present from oft-repeated episodes[1].

Although uniform episodes of abdominal pain had occurred with monthly regularity for 4 years interposed by several longer intervals of freedom, they have not recurred to date, 2 years after appendectomy. Whether or not episodes will resume remains to be seen. Other victims of periodic peritonitis have had similar long respites. They had occurred during pregnancy[1]; (case 10)[2]; during

confinement in a prison-camp[3]; after tonsillectomy[4], appendectomy[5], and spontaneously[6], (case 24)[7], but episodes resumed in their usual rhythm. In one instance, episodes had not recurred for 20 months after "cure" with ACTH[8]. The severity of symptoms in a few patients was lessened temporarily after cholecystectomy (case 9)[2], by therapy with cortisone (case 1)[7] and by Oxylone (fluoromethalone)[2].

Summary

A patient had had periodic peritonitis for 4 years. The last observed episode differed from former ones with pain beginning in the right lower quadrant after a shorter interval than usual. An inflamed, ulcerated appendix with mucosal involvement and pus containing *E. coli* was excised. Episodes ceased since then, but similar behavior had occurred in other patients with resumption of episodes many months later. Acute abdominal emergencies of other origin may arise in victims of periodic peritonitis and demand prompt diagnosis and treatment.

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ANORECTAL PATHOLOGY IN SYSTEMIC DISEASE

Report of a Case of Leukemia

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A proctologist who examines the anorectal area should at all times peer at the entire patient and quiz himself whether or not a systemic condition may be related to the anorectal lesion which he finds. This the more if the topical lesion is atypical and not of the sort he is used to seeing every day. Sigmoidoscopy in all cases and roentgen studies in some are completing this examination. His interest, though, will center on the anorectal area, but should fan out over the entire patient.

Walsh and Stickley[21] stated, "The specialist may be getting the first glimpse of a general disease, like a nose and throat man observing tonsillary enlargement or a dentist noting acute dental alveolar complications in leukemia". The two authors predict that the proctologist will advance in line to be first to recognize a systemic disease. As far as leukemia is concerned, it may be noted that there are a certain number of reports by nose, throat, and dental men; but very few reports by proctologists in the American literature[2,4,6,12,14]. Therefore, a narrowly encapsuled attitude which at times really exists is wrong. It may be illustrated by two independent statements of two respected authorities in the field. This is what they said to this author, and I quote: "The history and the symptoms are of no value in the diagnosis of anorectal disease; only the examination of the area will establish the diagnosis". The other one: "Having a good all-round medical training may make you a better doctor, but it does not make you a better proctologist".

This attitude in my opinion is a dangerous one. At last, I believe, I have the possibility of contesting these words with some experience. In recent years, I have had the occasion to report a few unusual cases in which local anorectal manifestations were closely linked with systemic diseases. While it is the present intention to refer to them only briefly, another more recent case report should be added in more detail. One of the cases was a bleeding tumorous lesion of the lower rectum which turned out to be an allergic manifestation[25], and simply vanished after conservative systemic antiallergic measures. One was a stricturing tumor of the anal canal, finally diagnosed as a rare tuberculous granuloma[26] which receded markedly upon appropriate systemic medication. One was a vesicorectal abscess and fistula and nonspecific anal granuloma as a result of a chronic enteritis[27]; one was a case of excessive bleeding upon excision of a

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thrombosed external hemorrhoid (note the discrepancy between spontaneous thrombosis and prolonged bleeding)[24] which turned out to be on the basis of a complicated metabolic and deficiency condition. None of these cases could have been properly managed without taking the entire system of the patient into account.

In the following a case will be reported in which the anorectal lesion was deceptive and detained the observer from arriving at the correct diagnosis for some time. The patient's general complaints had seemingly no relation to the anorectal disease and, therefore, did not get immediate proper attention.

The patient was a white woman of about 50 years of age. She was married and childless. In her first visit, which occurred four years prior to the events to be recorded here, she complained of a "pimple" near the rectum, of rectal pain, and little bleeding, drawing pain extending to both thighs, and urinary frequency. The examination was difficult because of pain and sphincter spasm. In the hospital, under general anesthesia, a fissure-in-ano and hemorrhoids were found and excised after sigmoidoscopy to 10 inches failed to reveal any further pathology or bleeding. The postoperative course was uneventful and after a few weeks of after-care, the patient was discharged.

As far as the anorectum is concerned, the patient was in good condition until she returned four years later. She complained of anal distress for the past two weeks. A "boil" had formed from which pus escaped. She also complained of general fatigue. Examination revealed elevation and induration of the area posterior to the anal opening. A fissure was embedded externally to the anal canal; not a fissure-in-ano as commonly seen. The sphincter was slightly spastic, but relaxed under the examiner's finger. An indurated bulging mass was palpated in the posterior aspect of the anus, immediately proximal to the sphincter muscle. Purulent material escaped. Anoscopy offered a peculiar sight: within the indurated area there was a cavity big enough to admit a finger. The distal opening looked as if it were starched and maintained a stiff, flat, oval cleavage. The lining of the cavity as far as it could be seen was grey-white granulous.

No similar lesion had been seen by this examiner previously; therefore, a consultation was requested. This is the result of the consultation, and I quote: "In my opinion this represents a chronic fissure resulting from a submucous abscess which has destroyed the overlying mucosa so that the musculature of the anal canal lies exposed. I do not find anything to suggest any malignant changes in the lining of the fissure. I believe that she (the patient) will require further surgery to effect a cure; however, I suspect that in view of her other problems continued palliative treatment is in order".

There is no doubt that this examination was a very thorough and conscientious one. It is to be noted, however, that other problems were mentioned in the report, but there was no suggestion of their possible importance in relation

to the anal disease. Two weeks of conservative measures followed, chiefly observation and palliative, the latter consisting of cleaning the lesion's cavity with peroxide and applying 10 per cent argyrol; bed rest and sitz baths. Discharge and local distress actually ceased; however, the patient continued to complain of general fatigue. By the end of the second week of observation her appearance clearly sustained her complaints: the face seemed to be small and the facial skin had a brownish-grey tint. A systemic disease was apparent. Blood count at this point revealed the following:

Hemoglobin: 40 per cent-6.8 gm.
Color index: 1,0
Erythrocytes per cu. mm.: 1,980.00
Leucocytes per cu. mm.: 4,400.
Polys. nonsegmented: 1 per cent.
Polys. segmented: 4 per cent.
Polys. eosinophils: 0 per cent.
Polys. basophils: 0 per cent.
Monocytes: 0 per cent.
Lymphocytes: 95 per cent.
Normoblasts: 18
Red cell morphology: Marked anisocytosis;
marked poikolocytosis;
marked polychromatophilia

On these alarming findings the patient was hospitalized as an emergency and turned over to a competent hematologist. His final diagnosis was: Acute, myelocytic leukemia. He did not have much hope for this patient who was treated with massive doses of metacorten. Response was slow, yet a few weeks of intensive treatment resulted in a definite improvement of her general condition and blood count. The anorectal lesion had practically receded. Sigmoidoscopy at this time was negative. After about four weeks, the patient was discharged from the hospital and directed into the office of the hematologist. A short time later, however, there was a relapse and the patient was readmitted to Polyclinic Hospital, where she expired after a few days. Unfortunately a postmortem was performed without including the anorectal area.

Summary

A few cases have been mentioned where anorectal lesions have been the result of a general systemic disease. One case of leukemia has been elaborated. In the beginning the anal lesion was the only manifestation of a blood dyscrasia.

Epitaph

The proctologist is a medical doctor. He should have sufficient general medical training to enable him to apprehend a systemic disease related to proc-

tologic lesions. An examination restricted to anorectal and colonic areas is not sufficient for diagnosis. We should be aware that we do not treat a localized lesion only, but the entire patient, for there may be, in some cases, a relation between the anorectal lesion and a disturbance of the system.

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TREATMENT OF ASYMPTOMATIC ENDAMEBA HISTOLYTICA CARRIERS WITH A FORMULATION OF BACITRACIN METHYLENE DISALICYLATE AND IODOCHLORHYDROXYQUIN (ANAMEBA)*

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Amebiasis, a protozoan infection caused by *Endameba histolytica*, is widespread throughout the world, occurring with greatest frequency in tropical and subtropical areas. Incidence of the disease in the United States has been estimated at 4 per cent of the general population, but may be higher in some areas than in others[1].

Surveys from different parts of the world have shown that many apparently healthy individuals harbor *E. histolytica* in their intestinal tract. A small number may develop mild intestinal symptoms or even severe amebic dysentery, but the greatest majority have no symptoms whatsoever, and consequently remain unnoticed and untreated, a permanent reservoir of the disease[2].

TABLE I

RESULTS OF PRETREATMENT STOOL EXAMINATION OF 135 PATIENTS

Ward	No. patients	Positive for *E. histolytica*	Positive for other protozoa	Positive for helminths	No parasites found
G	36	10	25	16	6
H	71	10	38	30	24
I	28	3	17	11	9
Totals	135	23	80	57	39

Note: A number of the patients harbored more than one form of intestinal parasite.

Amebic infection takes place after the ingestion of an *E. histolytica* cyst, which passes unharmed through the stomach and into the small intestine. During its passage through the small intestine or after its arrival in the cecum, the four-nucleated ameba emerges from the cyst. After excystation the normal four-nucleate ameba undergoes further division and single nuclei, with a portion of ectoplasm, separate into small actively motile amebae. This process of multiplica-

Louisiana State University School of Medicine, New Orleans, La.; State Colony and Training School, Pineville, La.

*The Anameba tablets used in this study were supplied by the Chicago Pharmacal Company.

tion takes place in the lumen of the intestine, where the trophozoite grows to full size. The amebae from the cecum may be carried in the fecal contents toward the terminal portion of the colon, undergoing encystation in preparation for survival outside the body of the host. The number of cysts voided by an infected individual may vary from 300,000 to 45 million per day, with an average of 14 to 15 million[3]. If conditions in the cecum and other areas of the large intestine are favorable for tissue invasion, the motile amebae may penetrate the wall of the intestine and produce lesions. These lesions and the tissue damage may or may not be extensive enough to produce acute symptoms.

Drugs cited by the Council on Pharmacy and Chemistry (1956) for the treatment of amebiasis include emetine, arsenicals, iodoquinolines (including iodochlorhydroxyquin), and certain broad-spectrum antibiotics. Among the antibiotics which have been studied carefully are bacitracin, carbomycin, chlortetracycline, oxytetracycline, chloramphenicol[4] and fumagillin[5]. Studies with bacitracin have shown little or no toxicity when used alone.

TABLE II

SCHEDULE OF TREATMENT AND POSTTREATMENT FOLLOW-UP FOR 23 CARRIERS AND 26 NONCARRIERS

24 February 1958:	Pretreatment examination of stools among 135 patients.
14-21 April:	Course of therapy for 23 patients positive for *E. histolytica* and 26 noncarriers
14 May:	First posttreatment stool examination for 23 infected patients.
29 May:	Second posttreatment stool examination for 13 patients in Wards H and I.
29 June:	Second posttreatment stool examination for 10 patients in Ward G.
23 July:	Third posttreatment stool examination for all 23 patients.
18 August:	Fourth posttreatment stool examination for all 23 patients.

METHODS AND MATERIALS

This study is concerned with the use of a formulation of bacitracin methylene disalicylate, purified, and iodochlorhydroxyquin (Anameba) in the treatment of asymptomatic carriers of *E. histolytica* at the State Colony and Training School, Pineville, La. Each tablet contains 125 mg. iodochlorhydroxyquin and 5,000 U.S.P. units of bacitracin activity in the form of bacitracin methylene disalicylate.

Bacitracin methylene disalicylate is a new complex of bacitracin. It was studied by Siminoff and co-workers[6] and was found to have the same antibacterial spectrum as bacitracin. Radomski and co-workers[7] reported that its margin of safety was similar to that of bacitracin, and Alvarez and Rivera

Torres[8] reported that the therapeutic qualities also were similar to those of bacitracin.

Bacitracin methylene disalicylate has been used successfully in the treatment of certain enteric diseases of swine, and has also been used in combination with carbarsone in the treatment of amebic dysentary in human patients.

A pretreatment stool examination of 135 patients at the Pineville institution showed that 23 were infected with *E. histolytica*, although they did not show any signs or symptoms of the infection (Table I). Seventy-three others harbored various other parasites, such as *Endameba coli, Endolimax nana, Trichuris trichiura, Ascaris lumbricoides, Strongyloides stercoralis,* and *Giardia lamblia.* No parasites were found in 39 patients.

Tablets of bacitracin methylene disalicylate and iodochlorhydroxyquin (Anameba) were given to 49 patients housed in three wards (G, H and I).

TABLE III

RESULTS OF FOUR POSTTREATMENT STOOL EXAMINATIONS FOR 23 CARRIERS OF *E. histolytica*

Ward	Positive at start of therapy	First posttreatment examination	Second	Third	Fourth
G	10	1	1	1	1
H	10	1	2	2	3
I	3	0	0	0	0
Totals	23	2	3	3	4

Twenty-three of this group constituted the positive carriers of *E. histolytica*; 26 others were not *E. histolytica* carriers, but were included in the treatment schedule to study possible toxicity and side-effects.

The dosage schedule called for the administration of one tablet three times daily after meals for eight consecutive days. All patients remained on their regular diet. Four posttreatment follow-up examinations were conducted in the succeeding months (Table II).

RESULTS

None of the 49 patients who received the combination of bacitracin methylene disalicylate and iodochlorhydroxyquin showed any evidence of unpleasant reactions. There was no nausea, diarrhea or other signs of toxicity or side-effects.

The first post-treatment stool examination of the 23 carriers was carried out approximately three weeks after the course of treatment was completed (Table III). Only 2 were still positive. This result is considered excellent, and compares

favorably with that of other drugs now being used for the treatment of this infection.

Results of treatment on Ward G are especially interesting. There was only one treatment failure in the group, and there were no relapses during the entire follow-up period of over three months.

On Ward H the first posttreatment examination revealed one positive. By the fourth posttreatment follow-up, there were three positives. It is quite probable that at least one and possibly two of the positives were reinfections rather than relapses.

On Ward I no positives were detected during any of the follow-up examinations.

Conclusions

Results of treatment with a combination of bacitracin methylene disalicylate and iodochlorhydroxyquin (Anameba) in a group of 23 carriers of *E. histolytica* were excellent. No toxic reactions or side-effects were noted among the 49 subjects who received the drug during an eight-day course of treatment. Additional studies with this agent should be made, particularly in acute cases.

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USE OF SULFADIMETHOXINE (MADRIBON®) IN ULCERATIVE COLITIS*

JOHN B. CHRISTODOULOPOULOS, M.D.†

and

ARTHUR P. KLOTZ, M.D.

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Although ulcerative colitis is generally difficult to treat because its etiology is obscure and it has no specific therapy, many patients can be helped to lead a relatively normal life by comprehensive medical management. Numerous medications, including a variety of sulfonamides, are currently used along with dietary restrictions. In 1939 Bargen[1] reported that neoprontosil resulted in better therapeutic results than those he had obtained previously with the use of a vaccine prepared from organisms isolated from the rectal mucosa of ulcerative colitis patients. Since then sulfathalidine, sulfasuxidine, and sulfaguanidine have been frequently used. Svartz[2] of Sweden reported encouraging results in 1948 using an azo compound of salicylic acid and sulfapyridine, commercially known as Azulfidine or Azopyrine. Bargen[3], one year later, introduced the drug to this country and stated that it was a definitely valuable adjunct in the therapeutic regimen of ulcerative colitis.

Synthesis of a new long-acting sulfonamide, 2,4-dimethoxy-6-sulfanilamido-1, 3-diazine (sulfadimethoxine), was achieved by Bretschneider and Klotzer[4] in 1955. This compound is known commercially as Madribon. Since it is a nontoxic sulfonamide quickly producing therapeutic blood levels that are maintained by a ½ gm. tablet daily, its use in the medical management of ulcerative colitis seemed worth evaluating. It has a broad-spectrum effect similar to recent antibiotics, being active against gram-positive and some gram-negative organisms. Azopyrine and sulfaguanidine, unlike sulfadimethoxine, must be used in large doses, often necessitating as many as 16-18 tablets daily. Steroids are frequently employed in treatment of ulcerative colitis today and management includes concomitant antibiotics such as penicillin and streptomycin. The relatively insoluble sulfaguanadine probably cannot substitute as the needed antibacterial in such cases. An absorbable, effective, single oral daily tablet such as sulfadimethoxine would seem to have certain advantages. This present study is concerned with the use of this sulfonamide in 30 patients with ulcerative colitis.

Materials and Methods

Thirty patients with different degrees of severity of ulcerative colitis were selected for this study. Outpatients as well as hospitalized patients were used.

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There were 18 males and 12 females. Ages ranged from 16 to 65 years. An initial dose of 1 gm. of sulfadimethoxine followed by 0.5 gm. daily was given to these patients. The duration of therapy ranged from 4 weeks to 1 year. Most of the patients received sulfadimethoxine for a period of six months. Three patients received the drug for 11 months and one patient over one year. Ten patients with acute ulcerative colitis received ACTH therapy during their hospital course. ACTH was given in divided dosages usually totaling 120 units daily over a period of weeks. Sulfadimethoxine served as the antibacterial medication in each of these cases. Other adjunctive measures in the treatment consisted of low-residue diets, antispasmodics, vitamins and sedatives. Measurements of free and total sulfadimethoxine in the blood and urine were assayed

TABLE I

SULFADIMETHOXINE LEVELS IN BLOOD AND URINE

Treat. Day	Blood mg. %		Urine mg. %		Urine volume Per 24-Hour	24-hour urine mg.	
	Free	Total	Free	Total		Free	Total
1	10.34	11.12	17.56	18.38	1250 c.c.	212.50	225.00
2	8.78	9.03	19.44	21.58	1170 c.c.	222.30	245.70
3	8.46	9.11	23.58	27.64	1200 c.c.	176.00	324.00
4	6.82	7.56	20.79	24.56	975 c.c.	195.00	234.00
5	6.45	7.76	22.51	27.64	1380 c.c.	303.60	372.60
6	5.67	6.80	19.58	25.32	870 c.c.	165.30	217.50
7	5.18	5.90	24.95	31.21	1100 c.c.	264.00	341.00
8	4.27	5.34	25.72	30.48	1350 c.c.	337.50	405.00
9	3.37	3.83	27.82	32.56	1020 c.c.	275.40	326.40
10	3.63	3.97	21.57	26.75	1280 c.c.	268.80	332.80
25	2.95	3.88	30.26	35.95	1000 c.c.	300.00	350.00
40	2.19	2.78	32.17	40.28	1200 c.c.	384.00	480.00

by the Bratton-Marshall method[5]. Fecal studies and quantitative stool determinations of the drug were also performed in nine patients.

RESULTS

All patients tolerated the medication without complaints and no side-effects were noted. Blood determinations showed a slow progressive fall of free and total sulfadimethoxine as administration continued. The results were similar to those reported by Ironson[6]. Typical findings of blood levels are shown in Table I. Such studies were performed in 15 patients. Quantitative stool and urine studies generally showed well over 50 per cent recovery (Table II). Cultures of fecal flora revealed minor changes which were not quantitated in this study. Stools of patients receiving penicillin and streptomycin while on steroids usually lose their offensive odor; this was not observed with sulfadimethoxine. General clin-

TABLE II

FECAL AND URINARY SULFADIMETHOXINE EXCRETION

Patients	Blood mg. %		Urine mg. %		Urine volume	24-hr. urine mg.		Stool total mg %	Weight of 24-hr. stool (grams)	Total mg. in 24-hour stool	Total mg. urine & stool	Recovery % urine & stool
	Free	Total	Free	Total		Free	Total					
1	2.94	3.86	19.58	27.42	970 c.c.	184.30	261.9	40.00	285	114.00	375.90	75.8%
2	2.48	3.05	22.74	30.05	1130 c.c.	256.96	339.6	48.56	190	92.26	431.86	86.4%
3	2.94	3.49	31.58	40.72	800 c.c.	252.64	345.76	29.52	90	26.56	372.32	74.5%
4	3.16	4.98	19.67	27.76	1150 c.c.	226.70	319.24	39.50	128	50.56	369.80	74 %
5	2.19	2.93	36.22	42.78	800 c.c.	289.76	342.24	36.15	144	52.05	394.29	78.8%
6								34.20	110	37.62		
7	5.94	6.67	19.48	22.03	1210 c.c.	235.71	266.59	43.75	95	41.56	308.15	61.6%
8	3.15	3.78	18.95	29.70	1240 c.c.	234.98	368.28	28.95	235	68.02	436.30	87.3%
9	3.38	3.99	16.42	25.56	710 c.c.	116.58	181.48	48.90	130	63.57	245.05	49 %

ical and proctoscopic improvement compared favorably with that occurring when other sulfonamides or antibiotics are used. The maintenance dose of 0.5 gm. daily (one tablet) is a great advantage as compared to other sulfonamides which usually are given in dosages of 8 or 9 gm. daily. In addition, the use of one tablet of sulfadimethoxine daily in place of parenteral antibiotics during steroid therapy is an advantage because of its simplicity. The absence of side-effects and toxic reactions on long-term therapy is essential in treatment for a chronic disease such as ulcerative colitis. Patients sensitive to penicillin can be given sulfadimethoxine as a satisfactory broad-spectrum antibiotic. Several of the patients in this study reported sensitivity to other sulfonamides but tolerated sulfadimethoxine without any reaction. A desirable constipating effect such as that sometimes seen with azulfidine or sulfaguanidine was not noted in this study.

Summary

1. Thirty patients with different degrees of severity of ulcerative colitis received sulfadimethoxine, a new long-acting sulfonamide, orally.

2. No evidence of side-effects or toxic reactions was demonstrated.

3. Sulfadimethoxine was used in place of parenteral antibiotics during intensive steroid therapy in 10 of the 30 patients.

4. Clinical response as compared to response with other sulfonamides or antibiotics was very satisfactory.

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President's Message

In this farewell message I would like to express my appreciation for the honor and the privilege of being permitted to serve as President of the American College of Gastroenterology.

The year has been a good one. There have been no major problems.

The American College of Gastroenterology has been making steady progress, but we have no reason to become complacent.

During the year I have made certain recommendations which I would like to reiterate.

I feel that regional meetings are a necessity and should be held at least once each year.

I have suggested that we should show a greater interest in our younger members, particularly those with organizational and leadership ability with rapid advancement into positions of responsibility.

I have recommended the publication of an annual review of progress in clinical gastroenterology.

I would like to call your attention to the immediate availability of funds for medical research. We must channel more of these funds into gastrointestinal research.

We must encourage more young men – recent graduates to enter the field of gastroenterology.

Medicine has made great strides. We have seen the introduction of the sulfa drugs, antibiotics, steroid hormones and the blood bank.

All of these contributions have aided materially in the practice of gastroenterology.

The decade ahead promises even greater discoveries of which we must avail ourselves to keep gastroenterology in the forefront of medical progress.

Jos. Shaiken

NEWS NOTES

Fellowship Keys

Keys for *Fellows* of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the key is at the left.

These may be ordered from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with your name and the date of your election to Fellowship. Send your order today.

In Memoriam

We record with profound sorrow the passing of Dr. Joseph P. Cangelosi, Chicago, Ill., Associate Fellow and Dr. Samuel Kalfus, New York, N. Y., Associate Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

ABSTRACTS FOR GASTROENTEROLOGISTS

ESOPHAGUS

PHARYNGOESOPHAGEAL DIVERTICULUM: Harold E. Dunlap, George Crile, Jr. and Laurence K. Groves. Cleveland Clin. Quart. 25:158 (July), 1958.

Pharyngoesophageal diverticulum is a herniation of pharyngeal mucosa and submucosa through a weak region in the musculature of the distal hypopharynx. It is rare and occurs predominantly in males in the fifth to seventh decade.

It may be seen with a barium swallow or on x-ray as a midposterior sac at the level of the 6th cervical vertebra.

When the diverticulum is small the symptoms are transient and intermittent and consistent of fullness in the throat and a sensation of obstruction. As the sac gets larger the patient may also have dysphagia, gurgling sounds, esophageal obstruction, dyspnea and regurgitation into the tracheobronchial tree.

The authors treated 37 cases surgically and concluded that large sacs are best treated by excision, the small ones by inversion and that either procedure is satisfactory for average size diverticula.

THEODORE COHEN

PEPTIC ESOPHAGITIS: Walter H. Maloney. J. Lancet 79:14 (Jan.), 1959.

Peptic esophagitis is usually due to damage of the esophageal mucosa from reflux gastric acid. Hiatus hernia is the most important etiologic factor. Forty per cent of cases have an associated peptic ulcer.

The pathology is that of diffuse chronic inflammation which may progress on to granulation tissue formation, ulcer and stenosis.

The symptoms vary from mild substernal pain and heartburn to dysphagia, hematemesis, melena, weight loss and secondary pulmonary complications from spillage into the tracheobronchial tree.

The diagnosis is made by history and x-ray studies, although early, the latter may be of little help. The finding of a hiatus hernia with a congenital short esophagus should make one suspicious of the presence of the clinical entity.

The therapy early consists of bland diet, antispasmodics, antacids and elevation of the head of the bed at night. In more severe cases esophageal dilatation and even partial gastrectomy with vagotomy may be indicated. With an adequate regimen approximately 80 per cent of patients should respond to medical treatment.

Although stricture formation is the most common complication, hemorrhage, perforation and mediastinitis are the more serious.

THEODORE COHEN

ACHALASIA OF THE ESOPHAGUS WITH PULSION DIVERTICULUM: William J. Pickett and W. M. Moss. Illinois M. J. 115:17 (Jan.), 1959.

Sweet describes two types of achalasia, both being characterized by absence of Auerbach's ganglion cells. Type I achalasia which accounts for 80 per cent of the total, is characterized by excessive dilatation of the esophagus with an atrophic lower segment and absence of pain, spasm or peristaltic activity. Type II achalasia accounts for the remainder of 20 per cent characterized by less dilatation of the esophagus and hypertrophy of the circular muscle layer of the lower segment and presence of substernal pain with spasm. Radiographic examination of type II achalasia reveals active but abnormal peristalsis.

JOSEPH E. WALTHER

STOMACH

CLINICAL TRIAL OF A NEW ANTICHOLINERGIC-TRANQUILIZER COMBINATION: Bert H. Leming, Jr. Clin. Med. 6:423 (March), 1959.

The author has written up the results of a clinical trial of a new drug (Enarax®) and according to him, this drug has the following advantages: integrated psychic and somatic management, low dosage requirement, flexibility of dosage (scored tablet), prolonged action, low incidence of side-effects, owing to postganglionic blockade, and a very favorable therapeutic index.

IRVIN DEUTSCH

OBSTRUCTING EOSINOPHILIC GRANULOMA OF THE STOMACH ASSOCIATED WITH ARTERIOMESENTERIC DUODENAL COMPRESSION: Meyer O. Cantor. J. Internat. Coll. Surgeons 31:281 (March), 1959.

A case report is presented of the presence of an obstructing eosinophilic granuloma of the stomach. This is believed to be the 36th such pathological state recorded in the literature. The salient features of this report in addition to the gastric symptomatology is that there was an associated neurological problem characterized by dizziness, and mental retardation. Following gastric surgery the patient's gastric and neurological complaints improved. The author stresses the fact that allergy may play a great rôle in this type of pathology. He also states that if the underlying pathology was known prior to surgical intervention, surgery can be avoided and conservative therapy instituted with steroids.

BERNARD J. FICARRA

ISCHEMIC ANASTOMOTIC BREAKDOWN AND GANGRENE OF THE GASTRIC REMNANT FOLLOWING SUBTOTAL GASTRECTOMY: Buford T. Casebolt. J. Internat. Coll. Surgeons 31:269 (March), 1959.

The author presents two cases of gangrenous degeneration of the gastric remnant following subtotal gastrectomy. The basis for the complication resides in the destruction of the blood supply to the gastric stump following extensive surgery. An avascular remnant is a potential complication that requires forethought in high subtotal gastrectomy especially when it is in association with splenectomy, vagotomy or hiatus hernia. In Billroth I resections it is advisable to preserve an adequate blood supply to the remnant, and to focus attention of duodenal mobilization rather than extensive gastric mobilization in order to obtain an anastomosis without tension. It appears that a high index of suspicion of an avascular remnant coupled with early reexploration and resection of the ischemic or gangrenous remnant would be the treatment of choice.

BERNARD J. FICARRA

SOME ERRORS IN THE DIAGNOSIS OF GASTROINTESTINAL NEOPLASMS: O. M. Jankelson. Rhode Island M. J. 42:163 (March), 1959.

The gastrointestinal tract has always been most stubborn in revealing the nature of its pathologic processes. The differentiation between a benign or malignant gastric ulcer, simple or benign polyp, has always been the enigma of the gastroenterologist. Errors in diagnosis are divided by the author into: delay of the patient to seek advice early in the disease and the failure of the physician to promptly institute steps to use all diagnostic tools available to reach a definitive diagnosis. A good history and physical followed by the proper diagnostic procedures such as roentgen study, gastroscopy, sigmoidoscopy, esophagoscopy, cytology and even surgical laparotomy when still in doubt, will bring to surgery early malignancies, with a better chance of 5-year cures.

Some of the suggestive signs and symptoms of early malignancy are unexplained fever, unexplained anemia, sudden change in bowel habits, and sudden changes in the digestive pattern, such as loss of appetite, belching, bloating after meals, nausea and general abdominal discomfort.

A. J. Brenner

INTESTINES

CHRONIC MIDGUT ISCHEMIA: G. E. Mavor and William Michie. Brit. M. J. 5095:534 (30 Aug.), 1958.

With the advent of arterial surgery, thrombosis of blood-vessels has become a condition amenable to surgery. It is therefore important to make an early diagonsis of ischemia of an organ, particularly when surgery can reach the lesion. The superior mesenteric artery often becomes chronically and partially obliterated, which, if not relieved by surgery may lead to mesenteric thrombosis and intestinal obstruction. It therefore behooves the physician to remember that as we get "angina pectoris" in the coronary occlusion, we may similarly get partial occlusion of the mesenteric vessels giving rise to "abdominal angina".

Abdominal pain, altered bowel habits and weight loss are a triad of symptoms which should make the physician think of chronic midgut ischemia. To this is further added blood in the stool and malabsorption. This is characterized by constant fatty stools.

Two cases are herein reported from Aberdeen Royal Infirmary, London, England. Both of these patients had chronic midgut ischemia which gave the above characteristic symptoms. The patients developed mesenteric thrombosis and ended fatally. Perhaps if it was suspected in the early stage, that partial ischemia of the midgut was present, some form of surgery might have been undertaken, and perhaps the outcome might have been more favorable.

Lionel Marks

PSYCHOSOMATIC ASPECTS OF ULCERATIVE COLITIS: Daniel Offer. Illinois M. J. 114:159 (Oct.), 1958.

The author has exhaustively reviewed the literature which concerns itself with the personality of the patient suffering with ulcerative colitis. The literature from 1875 through 1956 embracing the writings of some 24 different authors during this period reveals complete unanimity of opinion on the part of all of them that the disease is definitely associated with some psychophysiological personality in every instance. The true basis of the emotional conflict may find its origin in very early life or may be a result of some psychic trauma suffered later in life. In either instance, it may require great perseverance and study to uncover the real psychic problem.

Although it is conclusive that the psychic factor in ulcerative colitis is a part of the disease-complex, at the present time more controlled studies would be required to confirm the claim that there is such a thing as an ulcerative colitis personality.

L. K. BEASLEY

TREATMENT OF CHRONIC NONSPECIFIC DIARRHEA: A. M. Connell and T. D. Kellock. Brit. M. J. 5115:151 (17 Jan.), 1959.

A report is made of the treatment of a group of cases with nonspecific diarrhea. The etiology of the diarrhea was diverse, but they formed a symptomatic group with an undiscoverable organic lesion. Their patients presented bowel symptoms for at least six months, with loose watery movements, associated with abdominal discomfort. Barium meal, barium enema, and sigmoidoscopic examinations were all negative. There was no evidence of steatorrhea in their cases.

In the treatment of their cases, they used codeine and tricyclamol (a hypercholinergic drug). Using the number of stools passed per week as an objective measure of effectiveness of these drugs, they found that codeine reduced the number of bowel actions to normal, and decreased the urgency and precipitancy of defecation; whereas, the antispasmodic effect of tricyclamol failed to control the symptoms, and in many instances exaggerated them. Thus, codeine was found to be an effective symptomatic remedy for chronic nonspecific diarrhea.

ZACH. R. MORGAN

THE PROBLEM OF RECURRENT INGUINAL HERNIA: Amos R. Koontz. Texas J. Med. 55:156 (March), 1959.

The author believes that the high recurrence rate of inguinal hernias after surgery is attributable to poor teaching in medical school and lack of interest in intern and resident training in the unspectacular subject of hernia repair. This makes the young surgeon find his own method to which he often adheres to the detriment of the patient. Among the various procedures the thoughtful surgeon will select one that "fits the patient—without doing violence to the anatomy encountered but which makes the most of the tissues available for repair". For suture material the author condemns catgut for lack of tensile strength and uses silk or cotton. He warns against "cutting on the knot" as hazardous. Handling the sac is another important item discussed in detail as is the search for more sacs. Some recurrences are due to an indirect sac, or femoral sac, having been overlooked at the time a direct hernia was operated upon, or vice versa. After giving great care to such important subjects as removal of areolar tissue; reducing the size of the cord; closure of the internal ring, the author devotes a considerable section of his paper to the all overshadowing danger of postoperative tissue tension and stress. Relaxing side incisions, grafts and prostheses have their places as has proper anesthesia during, and avoiding vomiting, coughing, and straining, after the operation.

WALTER CANE

EVALUATION OF PLICATION IN THE TREATMENT OF PERITONITIS AND ITS AFTERMATH OF INTESTINAL ADHESIONS: Thomas B. Noble. J. Internat. Coll. Surgeons 31:286 (March), 1959.

The author reviews his technic of plication of the intestines in the treatment of peritonitis. In addition to his own procedure and published reports, he cites other surgeons who have reported success in the employment of plication procedures. The author points out that the operation of plication has been highly effective in reducing the mortality rate of advanced peritonitis from 100 to below 4 per cent. The author emphasizes the fact that as yet there is no effective alternative procedure for dealing with advanced peritonitis and its aftermath of intestinal adhesions.

BERNARD J. FICARRA

FEVER OF OBSCURE ORIGIN—THE VALUE OF ABDOMINAL EXPLORATION IN DIAGNOSIS: Joseph E. Geraci, Lyle A. Weed and Donald R. Nichols. J.A.M.A. 169:1306 (21 March), 1959.

Seventy patients in this category were given repeated interviews, laboratory tests, x-ray studies and trial runs of antibiotics and chemotherapeutic agents with negative results.

Culture studies of all fluids of the body done in multiple media, complement fixations, tissue culture and animal innoculation likewise yielded no specific findings.

In 30 patients there were no symptoms referable to the abdomen, 15 had subjective symptoms and 34 had objective symptoms.

At operation 21 malignancies of the various organs were uncovered, 15 specific infections, tuberculosis, liver abscess, brucellosis, histoplasmosis, 14 indeterminate granulomatous conditions of the organs were found and 6 miscellaneous diagnosis of periarteritis nodosa, common duct stone, Whipple's disease, mesenteric vein thrombosis.

In 10 of the malignancies no adenopathy was present, and nothing from the clinical picture could have established diagnosis of lymphoblastoma, 4 had cancer at the head of the pancreas without symptoms or enlarged livers, a diagnosis of Hodgkin's disease was made in one case.

Of the specific infection, tuberculosis, appropriate isoniazid, aminosalicylic acid and/or streptomycin will reduce fever in 80 per cent of the afflicted and other infections can be treated by indicated therapy.

Where fever baffles and the patient is ill, possibly with loss of weight, high sedimentation rate and progressive anemia, laparotomy should be considered, the risk is minimal, postoperative morbidity slight and the diagnostic results satisfactory.

J. Edward Brown

AN EVALUATION OF THE ANTERIOR RESECTION OF THE RECTUM AND LOW SIGMOID: Frank C. Wheelock, Jr., Giles Toll and Leland S. McKittrick. New England J. Med. 260:526 (12 March), 1959.

The authors have made a study in 90 patients to determine the frequency of recurrence of carcinoma in the anastomatic suture line. They have adopted 10 cm. of normal-appearing bowel below the carcinoma, measured *in situ*, at the operating table as the minimum margin. There was 32 per cent shrinkage of the specimen at the laboratory. Cases that were studied were those whose lesions were within 20 cm. of the anus, where the superior and middle hemorrhoidal vessels had been ligated during the operation, the anastomosis lay within 15 cm. of the anus.

Forty-eight specimens were found to be grade II, 18 grade III and 5 colloid carcinoma and 19 were not registered. Positive lymph nodes were present in 30 patients, 14 (47 per cent) of which were alive after 5 years and in 60 patients no positive lymph nodes were found of which 32 (53 per cent) were alive after 5 years.

The authors found recurrence of carcinoma at the suture line in 10 cases (11 per cent) of the 90 studies. The tumor was of grade III malignancy in 7 cases and grade II in 3. There were positive lymph nodes in only 2 of the patients. They use the explanation of Cole, who found viable-appearing cancer cells located in the lumen of the bowel 21 cm. from the tumor in 65 per cent of the patients, which are implanted in the anastomic site.

Most recurrences took place within a 2-year period and the patients did very poorly.

Saul A. Schwartz

ADENOMAS OF THE COLON AND RECTUM: E. R. Wasemiller. J. Lancet 79:89 (March), 1959.

The adenoma-cancer relationship, no doubt, has been the single most important stimulus in the development of present-day concepts of diagnosis and treatment of adenomas of the colon and rectum. In view of our present knowedge, it is generally accepted that benign mucosal adenomas are definitely premalignant lesions. Since the

ideal approach to the treatment of any disease is prevention, it is appropriate and imperative to stress the early diagnosis and treatment of benign rectal and colonic lesions.

ALVIN D. YASUNA

LIVER AND BILIARY TRACT

CAVAL CONTRAST RADIOGRAPHY: Laughlin. A.M.A. Arch. Int. Med. 104:402 (Sept.), 1959.

A cavagram, a contrast x-ray of the inferior vena cava, can be easily obtained by cannulating the femoral vein and injecting contrast medium. Such x-ray pictures may show primary caval obstruction by tumors usually renal carcinomas and by bland thrombosis, compression of this vessel by renal, adrenal, pancreatic and other right retroperitoneal masses. Hepatic enlargement, especially hepatic tumors and abscesses may deviate or compress the vein. Large venous tributaries are visible in conditions producing increased abdominal venous pressure. Only after prolonged vena cava occlusion will the vertebral plexuses be filled with contrast medium. Therefore, these plexuses will carry cancer metastases from the abdominal organs only rarely. Inferior vena cava obstruction seems to be associated with ST deviations in the electrocardiogram.

H. B. EISENSTADT

CORTICOTROPHIN AND ADRENAL STEROIDS IN LIVER DISEASE: A.M.A Arch. Int. Med. 104:469 (Sept.), 1959.

The use of steroids in hepatic diseases depends: 1. on an appetite-stimulating effect, 2. their decrease of inflammatory and granulomatous reactions, 3. their counteractions against immunological disturbances. They influence the liver function in various ways. They mainly decrease the serum bilirubin. However, also the bile acids are decreased which brings relief of pruritus. The improvement of various other abnormal liver tests is inconsistent. ACTH and steroids can only be considered a useful adjunct to liver therapy. They do not change the basic process and the natural history of the disease. They may be used in the management of severe acute infectious hepatitis or hepatic insufficiency and particularly in lupoid hepatitis. The substances have little or no effect in chronic hepatitis and cirrhosis. Wilson's, Gilbert's and Dubin Johnson diseases are not affected by ACTH and steroids.

H. B. EISENSTADT

AN EVALUATION OF THE INDICATIONS FOR EXPLORATION OF THE COMMON DUCT: Arthur M. Smith and Morton C. Wilhelm. Am. J. Surg. 98:606 (Oct.), 1959.

The authors have listed eight indications for exploration of the common duct. Four of these were considered "absolute indications" and the other four "relative indications".

Stones in the common duct were found in 63 per cent of patients having an "absolute indication" and in 32 per cent of those explored having one or more "relative indications".

High epigastric or subxiphoid pain, contrary to their original impression, is the least reliable of the "relative indications". The authors are of the opinion that exploration of the common duct is not indicated when this is the only relative indication, and their experience does not warrant any conclusion as to the value of turbid bile in the common duct as an indication for exploration, but this merits further study and evaluation.

When two or more of the relative indications are present, the authors believe that the probability of finding stones in the common duct is much greater, and exploration is usually indicated.

They are of the belief that one must certainly explore some patients in whom only small stones or only a dilated common duct are present. These patients will continue to require the exercise of judgment based on history, clinical, laboratory and operative findings.

CARL J. DEPRIZIO

PANCREAS

EFFECT OF ACTH AND ADRENOCORTICAL STEROIDS ON EXTERNAL PANCREATIC SECRETION IN MAN: David A. Dreiling, Henry D. Janowitz and Harold Rolbin. New England J. Med. 258:603 (20 Mar.), 1958.

Fifty-nine patients were studied of whom 28 had no symptoms of pancreatic disease and 31 with proved pancreatic inflammatory disease. The drugs used in this study were ACTH (40 mg.), hydrocortisone (100 mg.), and prednisolone (50 mg.). These observers noted a decrease in the flow of bicarbonate secretion, the rate of amylase production, and the rate of flow. They do not feel the changes are of such magnitude as to justify their use in the treatment of pancreatitis since their effect appears to be obtained by production of damage to the acinar tissue. The use of the hormones should be limited to cases of acute pancreatitis and those with adrenocortical deficiencies.

ABE ALPER

STUDIES IN CYSTIC FIBROSIS OF THE PANCREAS: Lucas L. Kulczycki and Henry Shwachman. New England J. Med. 259:409 (28 Aug.), 1958.

The authors surveyed a series of 386 patients with cystic fibrosis. Eighty-five, or 22.6 per cent, gave a history of rectal prolapse. In 16 patients, rectal prolapse was the presenting complaint of cystic fibrosis. In 3 cases the diagnosis of cystic fibrosis was made seven, eight, and ten years after this initial complaint.

The factors responsible for the high rate of rectal prolapse in these cases include increased intraabdominal pressure, voluminous feces containing poorly digested foods, frequent movements, poor muscle tone, and general malnutrition, distention and relaxation of the large bowel, and occasionally the added increased intraabdominal pressure due to pulmonary emphysema, coughing and dilated small intestine. The treatment is medical, primarily a high protein and reduced fat intake combined with pancreatic replacement therapy, plus antibiotics to control pulmonary infection. The earlier the diagnosis of cystic fibrosis, the less likelihood of rectal prolapse.

SAMUEL M. GILBERT

ISLET CELL TUMOR OF THE PANCREAS: George R. Dillinger, C. H. Watt, Jr. and W. Vance Watt. J. M. A. Georgia 47:384 (Aug.), 1958.

A case history of a 43-year old white female who was admitted to the hospital in an unconscious state is presented. The patient presented a history of similar episodes over the past two years. The blood sugar was 28 mg. per cent, and pancreatic islet cell tumor (insuloma) was found at surgery.

The discussion of hyperinsulinism pointed up several salient factors to be considered.

Firstly, a blood sugar determination should be done in every unconscious patient, and in patients who manifest bizarre symptoms, especially if these symptoms are periodic in nature and are relieved by eating.

Whipple's Triad, i.e., attacks occurring during fasting state; blood sugar of 50 per cent or less; and relief of symptoms by administration of glucose, is diagnostic of insuloma. For borderline cases, tests involving periods of fasting up to 72 hours have been devised, with the findings of a blood sugar value of 45 mg. per cent or less, and hypoglycemic symptoms relieved by sugar administration as diagnostic. A provocative diet for 2 days of 1,200 calories with 50 gm. each of carbohydrate and protein followed by fasting for the third day, including 2 hours of vigorous exercise that day, has been employed by Conn and Selzer.

The authors conclude that about 90 per cent of cases of organic hyperinsulinism are due to benign functioning islet cell adenomas; and, that at surgery, though no tumor is visible, the body and tail (¾ of the organ) should be resected, because most functioning tumors are found in these areas. Also,

due to the fact that hyperinsulinism suppresses normal islet cell function, close supervision is mandatory to control the postoperative diabetic state which usually supervenes.

EZRA J. EPSTEIN

PATHOGENESIS OF PANCREATITIS: Edwin R. Fisher. Am. Pract. & Digest. Treat. 9:1253 (Aug.), 1958.

Acute pancreatitis is related to activity of pancreatic enzymes, trypsin and lipase, but no single causative factor is applicable to all instances of the condition.

However, acute pancreatitis has a common denominator, destruction of pancreatic parenchyma with release of enzymes into the tissue, and it may be that several of the above conditions must operate in conjunction to cause the acinar damage.

J. EDWARD BROWN

FIBROCYSTIC DISEASE OF THE PANCREAS: Edwin F. Hirsch. Illinois M. J. 114:178 (Oct.), 1958.

Fibrocystic disease and other nutritional disorders have been diagnosed clinically as celiac disease. According to Andersen, the term applies to a clinical syndrome, not to a disease entity, and symptoms can be produced by several disorders, one of which is the cystic fibrosis of the pancreas.

The main pathologic changes of fibrocystic disease or fibrosis of the pancreas, according to Andersen and others are: 1. replacement of acini of the pancreas by epithelium lined cysts embedded in fibrous tissues and without changes in the islets of Langerhans; 2. bronchitis, bronchiectasis, abscesses and bronchopneumonia of the lungs; 3. symptoms of Vitamin A deficiency in children who die within the first year of life; and occasionally, 4. atresia of the small bowel or of the cystic or pancreatic ducts. The cause of the lesions in the pancreas and in the lungs is not known; they probably are present at birth.

Clinical diagnosis can be difficult, especially before symptoms of pulmonary disease appear. The most direct method of diagnosis of functional deficiency of the pancreas is the assay of the pancreatic enzymes in the duodenal fluids. Technical difficulties may compromise the results with this procedure. An evaluation of these pancreatic enzymes indirectly by analyses of the blood for absorption products, following test meals of protein (gelatin), Vitamin A, and fat (cream) afford less troublesome laboratory methods for diagnosis. The chemical evaluation of the degree of a postprandial hyperlipemia by estimations of the esterified fatty acids of the blood in laboratories equipped to make these analyses, is relatively simple procedure for demonstrating normal or hyposecretion of pancreatic enzymes into the bowel.

A case report of a male patient, age 13, with the autopsy findings is presented in detail.

CARL J. DEPRIZIO

PANCREATITIS: J. Ned Smith. Missouri Med. 55:1084 (Oct.), 1958.

This is a review of the embryology, physiology and pathology of the pancreas. The majority of patients with pancreatitis have one of the three predisposing factors: alcoholism (present in 50 per cent), biliary tract disease (in 40 per cent) or trauma including surgery. Pain from the head of the pancreas radiates to the right upper quadrant, pain from the body radiates to the epigastrium, and pain from the tail to the left side of the abdomen. Pain is often preceded by a large fatty meal or an alcoholic bout. Confirmation of the diagnosis is obtained by the serum amylase test, which may be repeated daily if necessary.

Treatment is medical primarily, and consists of measures to rest the pancreas (nothing by mouth, Wangensteen suction, anticholinergics), relieve pain (nitrates, demerol) and combat infection (antibiotics). Surgery is useful for the drainage of cysts and abscesses. If the biliary tract is involved cholecystectomy and common duct drainage may be advisable. At times incision of the sphincter of Oddi may be done, and occasionally partial pancreatectomy.

ARNOLD STANTON

POSTGASTRECTOMY PANCREATIC SECRETION: (DIETARY MANAGEMENT OF PATIENTS WITH POSTGASTRECTOMY SYNDROME): Minoru Hirota. Yokohama M. Bull. 9:409 (Dec.), 1958.

An external pancreatic fistula following gastrectomy has given an opportunity for observations, the results of which, were applied to a series of patients with postgastrectomy syndrome.

This syndrome was divided into the early symptoms manifested by a sense of epigastric fullness, palpitation, perspiration, and in some by nausea, vomiting, abdominal pain and diarrhea; and late symptoms similar to typical "hypoglycemia", occurring three to four hours after meals and characterized by hunger, weakness, perspiration, palpitation and tremor. In the author's patient with an external pancreatic fistula he noted that the secretion of pancreatic juice began about 20 minutes after the start of the meal and continued for approximately 1 hour. He noted that glycine caused the pancreatic secretion directly. Starch, glucose, casein, B-alanine, glutamic acid, etc., stimulated the pancreas indirectly through gastric secretion. Mandarin orange had the greatest secretagogue effect on the pancreas among the fruits. It was noted that a mandarin orange 30 minutes before meals prevented late postgastrectomy syndrome from occurring in the majority of patients.

His results as published are in generalities and documentation of accurate results is lacking.

GLENN S. ROST

ACUTE PANCREATITIS: A. V. Pollock. Brit. M. J. 5113:6 (3 Jan.), 1959.

A detailed analysis of 100 patients admitted to the General Infirmary, Leeds, in the past 6 years is presented. A stone impacted in the ampulla of Vater was found in 5 of 26 patients who died and in one operative case. Fifty-six cases were correctly diagnosed by clinical picture and serum amylase elevation; 9 cases incorrectly diagnosed until autopsy, and 35 cases incorrectly diagnosed until laparotomy. There were 71 female and 29 male patients. The youngest was 6 years old. One-half of the men and three-quarters of the women had abnormal gallbladders, usually cholecystitis with stones. In some there was cholecystitis without stones. There were no cases due to alcohol. Other rare causes were trauma, pancreatic cancer, sphincterotomy. Twenty-five had had similar previous attacks. The general and local effects are considered primarily due to liberation of large quantities of active pancreatic enzymes into tissues and blood stream. ECG showed abnormality of T wave or ST depression in 19 of 36 cases, leading to a provisional diagnosis of infarction of myocardium in 2. Flat abdominal x-ray plates were normal in 29 of 38 taken. Three cases showed paralytic ileus on x-ray, and 2 cases elevation of diaphragm. Oral cholecystograms were abnormal in 30 of 38, and I.V. cholangiography with biligrafin showed abnormalities in 3 of 6. Barium meal x-ray examination was of value. Twenty-six were so studied. Eight showed a retrogastric mass, due to cyst in 6 and edema in 2. Five showed abnormal pattern of stomach or duodenal mucosa. Mucosal edema in one simulated carcinoma of the stomach. In one upper jejunal obstruction was found due to adhesions to necrotic plaques. The "papillary sign" was seen in 2. Serum amylase values over 600 Somogyi units were found in 71 patients with acute pancreatitis. In 16 others values did not exceed 600. There was no correlation of the serum amylase level with mortality. There were, in the same period, 34 patients without pancreatitis who had elevations of 200 to 600 units, and 8 cases without pancreatitis with values over 600. Two of the latter had proved myocardial infarction. Acute intra-abdominal disease was present in the others. Thirty-two patients were jaundiced. The serum calcium was between 8.5 and 11 in 30 with 4 deaths, and between 6.5 and 8.2 in 6 with tetany and death in all. Other serious complications were electrolyte disturbances, uremia, and hypoproteinemia, 3 cases had hematemesis or melena, due to gastric ulcer in one and undetermined cause in the others. Twelve cases had a mass. Fifteen of 65 patients treated conservatively died, as did 6 of 30 operated upon in the first week. Five were moribund on admission. Basic principles were used in treatment. Pain usually subsided rapidly on rest and analgesics. Antispasmodics were

without benefit, and the effects of corticoids is being evaluated. It is better to wait 6 or 8 weeks before operation for cyst formation. The author found the simple operation of transgastric anastomosis of the anterior cyst wall to the posterior gastric wall effective in 5 cases. Barium meal x-rays showed no trace of cystogastrostomy after as short a period as one week.

A high percentage of those recovered had no further attacks or suffered few after effects.

ERNEST LEHMAN

SPLEEN

DIFFERENTIAL DIAGNOSIS OF RUPTURE OF THE SPLEEN: Lester I. Goldsmith. Clin. Med. 5:157 (Feb.), 1958.

Splenic rupture may occur spontaneously in a normal spleen. More often it is traumatic and follows 6-31 days after a slight trauma of either the right or left side of the chest or upper abdomen. Spontaneous rupture occurs more frequently in a diseased spleen, particularly with malaria and infectious mononucleosis but it is also seen in the presence of any splenomegaly such as occurs with splenic infarction, abscess, tumor, infectious diseases, leukemias and lymphomas. Delayed traumatic rupture appears as a splenomegaly of unknown origin and may be asymptomatic. Usually, however, there is a pain in the entire abdomen or in the left upper quadrant irradiating to the shoulder. In addition, there is peritoneal and diaphragmatic irritation, shock, progressive anemia and abdominal fluid accumulation. X-ray shows obliteration of splenic shadow, diffuse density in the left upper quadrant displacing the neighboring organs and dilation of the stomach with gas and serration of its greater curvature. Differential diagnosis includes abdominal aneurysm, rupture of a Graafian follicle or of a corpus luten cyst, pancreatitis and rupture of the gallbladder. Splenic diseases most frequently confused with rupture of the spleen are thrombosis of the splenic vein, torsion of the splenic pedicle and splenic infarction.

H. B. EISENSTADT

TORSION OF A WANDERING SPLEEN: W. Shepherd Wilson. Central African J. Med. 4:299 (July), 1958.

The acute abdomen in the African is full of the unexpected, and any surgeon attacking the abdomen must be prepared for whatever he finds. The case reported here is of an African female, age 16-17 years. She was admitted to the clinic with severe abdominal pain situated in the right iliac fossa, of two days' duration, and was herself unable to give any history, but this was obtained from the mother. On examination, the respirations were very rapid and shallow and the pulse 150. The temperature was 97°F. There was fullness in the upper part of the right iliac fossa and on palpation there was acute tenderness and marked muscle guarding. A provisional diagnosis of acute appendictis was made.

At operation, the abdomen was opened through a lower right paramedian incision. The peritoneal cavity contained a quantity of blood-stained fluid and a mobile tumor. The incision was extended upwards and the tumor delivered. It was then found to be the spleen, having attached to its under surface a pedicle containing the splenic vessels, and a strong attachment of mesentery from the transverse colon. The spleen was in the abdominal cavity to the right of the umbilicus with its lower pole lying in the right iliac fossa in direct contact to the uterus and right fallopian tube. The pedicle containing the splenic vessels also contained pancreas and was twisted several times. There was no sign of gangrene of the intestines, although coils of small intestine were found to be rather hyperemic and dilated. The right fallopian tube was bluish-black in color and there was a considerable amount of plastic peritonitis on it and on the uterus. A portion of the right fallopian tube was removed. The pedicle of the spleen was ligated and cut. The attachment of the mesentery to the spleen was also severed. The appendix was behind the cecum, but revealed no evidence of recent inflammation. A drain was inserted

and the wound closed. The patient withstood the operation well, but four hours later, collapsed and died, cause undetermined.

A description of the specimen is given and the postmortem report. This adds another cause of pain, although infrequent, in the right lower quadrant, to the long list, for differential diagnosis.

CARL J. DEPRIZIO

PATHOLOGY AND LABORATORY RESEARCH

IMMUNOSEROLOGICAL STUDY IN INFECTIVE HEPATITIS: Sukeo Yamamoto. Osaka City M. J. 4:79 (June), 1957.

Employing various complement-fixation tests patterned after the various Wassermann reactions and hemagglutination inhibition tests the author claims to have demonstrated specific antibodies in the sera of patients with acute chronic hepatitis and hepatic cirrhosis. He believes that they are autoantibodies produced against the patient's destroyed liver tissue. The serological tests were positive in 70 per cent of acute and 60 per cent of chronic virus hepatitis and in 80 per cent of cases with cirrhosis. The antibodies belong to the gamma globulin fraction of the serum. Their titer fluctuated with the severity of the disease the highest titer was obtained 4 to 6 weeks after onset of acute virus hepatis. The antibody persisted in cases of chronic viral hepatitis and hepatic cirrhosis of the postnecrotic type.

H. B. EISENSTADT

A SUSTAINED-RELEASE BELLADONNA PHENOBARBITAL COMBINATION IN THE TREATMENT OF GASTROINTESTINAL DISORDERS: Gerald S. Backenstoe. Pennsylvania M. J. 69:983 (Aug.), 1957.

A two-year clinical study of sustained-release capsules containing belladonna alkaloids and phenobarbital was conducted on 64 patients suffering from various gastrointestinal and cardiovascular disorders. Stress symptoms were invariably present, often as the primary manifestation of disorder. Results were obtained as follows: excellent response, 35; good, 8; fair, 3; poor, 12; insufficient findings to evaluate, 6. Four patients experienced one of the following side-effects: dermatitis, dizziness with diarrhea, drowsiness, dermatitis with tachycardia. It was concluded that the marked clinical success of the sustained-release capsule in counteracting symptoms of parasympathetic stimulation indicates that it is of considerable value as a supportive medication for gastrointestinal and cardiovascular complaints.

ARNOLD L. BERGER

AMINO ACID MIXTURES IN THE TREATMENT OF EXPERIMENTAL DIETARY CIRRHOSIS IN THE RAT: Saul I. Cohn, Ernest Schmatolla, Margaret Bevans and Arthur J. Patek, Jr. A.M.A. Arch. Int. Med. 101:291 (Feb.), 1958.

Cirrhosis of growing rats can be produced by a diet deficient in protein as well as choline and methionine. Experiments in cirrhotic rats revealed that methionine had a marked lipotropic effect. Choline also had a lipotropic action by sparing methionine. Both substances, however, were not sufficient to produce a repair or regeneration of the cirrhotic liver. This could only be achieved by adding an amino acid mixture and still better by adding intact protein (Casein). These studies suggest that the factors governing fat deposits in the cirrhotic liver may be independent from those responsible for liver cell degeneration and regeneration. Apparently, various other amino acids have to be added to choline and methionine to reverse the process of cirrhosis in rats.

H. B. EISENSTADT

NITROGEN METABOLISM AFTER PORTACAVAL SHUNTS IN PATIENTS WITH CIRRHOSIS: Thomas C. Chalmers, Carl W. Hughes and Frank L. Iber. A.M.A. Arch. Int. Med. 101:434 (Feb.), 1958.

In order to evaluate the dangers of ammonia intoxication after shunt operations a group of 13 patients were studied who had either portacaval or splenorenal anastomoses. The blood ammonia concentration showed a marked rise during the first week after the operation; however, the blood levels returned to preoperative values by the 2nd postoperative week. This suggests that the elevation during the first week was merely a reflection of the impairment of postoperative liver function rather than a direct result of the shunt. All ammonia determinations in these studies were performed during the fasting state. Higher blood ammonia levels have been found following intake of a protein meal. However, these levels apparently are not sustained.

H. B. EISENSTADT

A COMPARISON BETWEEN THE ENZYME PATTERNS (GOT, GPT, LD) IN SERUM AND TISSUE EXTRACTS IN CARDIAC AND HEPATIC DISEASES: S. Linde. Scandinav. J. Clin. & Lab. Invest. 10:303 (Mar.), 1958.

Three enzymes, serum glutamic-oxalacetic transaminase, serum glutamic pyruvic transaminase and lactic - dehydrogenase were investigated during attacks of myocardial infarction and liver disease. In myocardial infarction the SGOT and SLD activity was found to be increased while the SGPT level was normal or only slightly increased. The same enzyme proportion was found in fresh striated muscle. This indicated that they were released by destruction of heart muscle into the circulation. Similarly, in liver poisoning and chronic alcoholism the SGOT activity was much more increased than the SGPT and SLD activity. This corresponded to the enzyme contents of normal liver tissue. However, a different enzyme pattern was found in epidemic hepatitis where the SGPT increase was much more pronounced than that of the other enzymes so that a different mechanism must be operating in acute hepatitis. This unusual enzyme abnormality remains to be explained.

H. B. EISENSTADT

INVESTIGATIONS IN A CASE OF MURDER BY INSULIN POISONING: V. J. Birkinshaw, M. R. Gurd, S. S. Randall, A. S. Curry, D. E. Price and P. H. Wright. Brit. M. J. 5094:463 (23 Aug.), 1958.

The authors report a case in which a male nurse murdered his wife by injecting her with insulin. She was three months' pregnant and the husband claimed he had injected ergometrine maleate to produce an abortion.

The same aspirates are examined cytocases there were 2 false positives. The five-

The corpse, found in the bathtub, was lying as though asleep and there was no evidence of splashing or violence. While death was caused by drowning, the medical examiner became suspicious as he was unable to explain why a healthy, young woman should drown in her bathtub without a sign of reaction to inhaled water.

Four hypodermic injection marks were found, two in each buttock. A biopsy of skin, fat, and muscles which included the hypodermic marks was removed from each buttock. These were refrigerated without any preservative at 4° for 15 days and were then examined for their insulin content. As no common poisons were found in the tissues of the body or urine, the finding of vomited food, sweat soaked pajamas, and the fact that the pupils were dilated, led the examiner to suspect the woman was hypoglycemic. Eighty-four units of insulin were recovered.

The many problems which arose during the medical and scientific investigations are fully discussed. On these findings the husband was found guilty and sentenced to life imprisonment.

ZACK R. MORGAN

DIAGNOSIS OF CARCINOMA OF THE PANCREAS, BILIARY TRACT, AND DUODENUM BY COMBINED CYTOLOGIC AND SECRETORY METHODS: Howard Raskin. Illinois M. J. 114:64 (Aug.), 1958.

Most carcinomas of the gastrointestinal tract are relatively easy to diagnose; however, carcinomas of the pancreas (including the duodenum and biliary tract) produce difficult diagnostic problems – this type of carcinoma is more common than has been stated. Raskin advocates a combined secretory and cytologic method of examination. A double lumen Diamond tube is passed through the mouth, with proper sequential changes of position of the patient which are described, the tube passes into position into the duodenum in 15 minutes and only one fluoroscopic check is required. Secretin is used as a stimulant of pancreatic secretion.

In carcinoma of the pancreas the pressure of the tumor on the pancreatic ducts produces sufficient atrophy to reduce over all volume without as a rule reducing bicarbonate concentration; in chronic pancreatitis the secretory functions are mainly affected accounting for depressed bicarbonate values whereas the volume may be normal.

The same aspirates are examined cytologically. When both tests were applied a successful diagnosis was obtained in 85 per cent of proven cases. In the cytological study alone 60 per cent of cases were proved by this method. In a total of 55 cases there were 2 false positives. The five-year survival of patients with carcinoma of the head of the pancreas is less than one per cent. It is still too early to tell whether the use of the combined cytologic and secretory methods has saved human lives.

SAMUEL L. IMMERMAN

CONDITIONED SECRETORY RESPONSE OF THE STOMACH FOLLOWING REPEATED EMOTIONAL STRESS IN A CASE OF DUODENAL ULCER: David C. H. Sun, Harry Shay, Barney Dlin and Edward Weiss. Gastroenterology, 35:No. 2 (Aug.), 1958.

This is a very interesting and probably important study in a single case of duodenal ulcer. More of this type of study may lead us to have insight into recurrent attacks in our duodenal ulcer patients. Thirty-four gastric secretory studies were made in this patient in which an ulcer was definitely known to exist. After basic studies were made, the patient was psychologically provoked and further secretory studies were made. The rage initiated by the psychiatrist soon caused a gastric hypersecretion response. This response began to behave as a conditioned reflex. There was a hypersecretion even when the psychiatrist was expected. In this way the patient behaved similarly to Pavlov's conditioned animals. It took approximately four weeks for the patient to get relief of the hypersecretory reflex once it was initiated. An anticholinergic agent or an andrenergic blocking agent could depress the hypersecretory reflex. Emotional adjustment could be made so that the interview no longer acted as a stimulus to hypersecretion. This experience is unique in that if one thinks of this experience in relationship to recurrent ulcer cases, we may begin to understand the cause of the ulcer cases flare ups.

LIONEL MARKS

NEWER LIVER FUNCTION TESTS: Stuart Ragland, Jr. Am. Pract. & Digest Treat. 9:1281 (Aug.), 1958.

Three new liver function tests based on catalytic action have been devised that promise help in evaluating hepatic damage.

The first depends upon hydrolysis of buffered acetylcholine by cholinesterase of patients' serum, results expressed by the change, delta pH units per hour determined colorometrically.

A norm of 0.5 delta pH units per hour has been established.

It must be stated that the test is of no value in early disease as cholinesterase level will maintain itself for about a week after the onset of pathology.

In portal cirrhosis the valuation of cholinesterase is of the utmost importance – prothrombin time may be 35 per cent of normal, serum albumin 2.8 gm. per cent and globulin 3.4 gm. per cent, a picture long conceived to be adequate for recovery

but if cholinesterase level shows but 0.19 delta pH units, the patient will die in a few weeks; if it be between 0.25 and 0.35 delta the condition is critical; if above 0.35 delta enough liver reserve is present for remission of the attack.

The test is not diagnostic it simply shows the amount of parenchyma damage.

The other two tests are:

Alpha-ketoglutarate plus L-Aspartate to Glutamate plus Oxalacetate.

The measurement of serum glutamic-oxalacetic transaminase.

Alpha-ketoglutarate plus L. Alanine to Glutamate plus Pyruvate.

The measurement of serum glutamic pyruvic transaminase.

Both tests are colorometric determinations and are expressed in Sigma-Frankel units; the first, SGOT as 8 to 40 units per ml. of serum; the second, SGPT as 5 to 35 units per ml. of serum.

The great value of these two tests lies in the rapid rise of SGOT and SGPT in hepatocellular damage by toxins, infections or serum hepatitis, often reaching above 2,000 units.

J. Edward Brown

DETECTION OF ANTIGENS IN SERA OF PATIENTS WITH NEOPLASTIC DISEASE BY SCHULTZ-DALE TEST: Jack G. Makari. Brit. M. J. 5092:358 (9 Aug.), 1958.

Preparation of guinea-pig sera with smaller volume antigens was used in an attempt to prepare a screening test for all tumors, including benign, and premalignant as well as malignant growths. Where positive tests occur, and no localizing evidence is found, further study to detect antigens from damaged organs by using sera from guinea-pigs immunized by normal organ tissue, can be carried out. Very favorable statistics for accuracy using 566 individuals and 704 serum specimens from the blood bank are reported.

Bernard Farfel

A CONTROLLED STUDY OF THE EFFECTS OF L-ARGININE ON HEPATIC ENCEPHALOPATHY: T. B. Reynolds, A. G. Redeker and Paul Davis. Am. J. Med. 25:359 (Sept.), 1958.

The effect of L-arginine on the clinical state and arterial blood ammonia level of patients with encephalopathy due to hepatic failure was compared with that of a placebo solution by the double-blind method. Marked clinical improvement followed arginine administration in only two of 34 instances and followed placebo administration in one of 26 instances. Mild or moderate improvement accompanied an additional 24 per cent of the arginine infusions and 35 per cent of the placebo infusions.

The mean arterial ammonia level was 180 mg/100 c.c. before and 160 mg/100 c.c. after administration of arginine. The difference between the means is not statistically significant.

There was some correlation, although not a close one, between the level of arterial ammonia and the severity of the encephalopathy.

A beneficial effect from L-arginine could not be demonstrated in this study.

John M. McMahon

LEUCINE AMINOPEPTIDASE ACTIVITY: Alexander M. Rutenburg, Julius A. Goldbarg and Esteban P. Pineda. New England J. Med. 259:469 (4 Sept.), 1958.

According to the authors leucine aminopeptidase is a proteolytic enzyme that is widely distributed in bacteria, plants and animal tissues, especially in the duodenum, kidney and liver. Its substrates are L-leucyl peptides. It has been demonstrated in gastric juice, bile and duodenal secretion, in pleural, peritoneal and spinal fluid, and in urine and serum. This report deals with serum and urinary activity of leucine aminopeptidase in patients with cancer of the pancreas, malignant lymphoma and leukemia, other cancers and control groups of normal persons as well as patients with nonmalignant conditions.

All patients with cancer of the pancreas showed a significant increase in urinary and serum leucine aminopeptidase. Patients

with cancer not involving the hepatobiliary tract had normal serum levels. Smaller and less persistent elevations were produced by common duct stone. Acute pancreatitis and cholecystitis caused only low grade transient elevations. Patients with malignant lymphoma or leukemia had increased urinary activity but normal or only slightly elevated serum levels. It would appear that the level of enzyme activity in serum and urine is of value in the early diagnosis of pancreatic cancer. Assays of leucine aminopeptidase are especially definitive, when normal, in ruling out cancer of the head of the pancreas.

LOUIS A. ROSENBLUM

EXPERIMENTAL STUDIES WITH P^{32} ON ABSORPTION FROM ALIMENTARY TRACT: Eiichi Ogawa and Senjiro Itagaki. Gunma J. M. Sc. 7:207 (Sept.), 1958.

Using radioactive phosphorus as a tracer, the authors studied the absorption of various substances from the alimentary tract of mice. The absorption of P-32 was highest in the small intestine, followed by the cecum, stomach and large intestine in descending order. Studies showed that the uptake rate of P-32 was decreased in the groups treated with morphine, chlorpromazine, pentothal, atropine and hexamethonium. The uptake rate of P-32 was not significantly changed by strychnine, picrotoxin, epinephrin and pilocarpine.

ARNOLD STANTON

PHYSICAL ACTIVITY, EMOTIONS, AND HUMAN OBESITY: Albert Stunkard. Psychosom. Med. 20:366 (Sept.-Oct.), 1958.

The authors studied physical activity as related to obesity by means of the Pedometer.

They found that physical activity was determined by emotional factors and could be reduced by patients having a depressive reaction pattern. They conclude that decreased physical activity and depressive reaction states may actually be the cause of obesity.

ABE ALPER

STUDIES ON BILE PIGMENT IN BILE. I. FLUCTUATIONS OF THE BILIRUBIN CONTENT IN LIVER BILE AFTER THE OPERATION FOR VARIOUS BILIARY TRACT DISEASES: Tomonobu Sato. Tohoku J. Exper. Med. 68:285 (25 Oct.), 1958.

The author utilized T-tube drainage in 25 patients (13 with gallstones, 5 with stoneless cholecystitis, and 7 with ascariasis of the biliary tract) and the bilirubin content of the liver bile was studied on the 1st, 2nd, 3rd, 5th, 7th, 10th and 14th days after operation. It was noted that the liver bile was of a yellowish, deep brown color for several days after operation and after 10 to 14 days was more dilute and light yellowish in color. The author called this "the postoperative bilirubin curve of liver bile".

Various theories were advanced for this response – none of which the author could conclusively prove. Some of these were:

Liberation of extravasated blood in large quantity with hemoglobin causing the bilirubin excess; or a febrile response in the period immediately after surgery.

Complete clarification of this change of bilirubin concentration of the bile will require future investigation.

MORTON SCHWARTZ

ANTICHOLINERGIC DRUGS. SURVEY OF THE LITERATURE AND SOME EXPERIMENTAL OBSERVATIONS: William H. Bachrach. Am. J. Digest. Dis. 3:743-799 (Oct.), 1958.

In an attempt at "realistic assessment", the author and his work deserve equal commendation for thoroughness of study and for forthrightness of conclusions. In witness of thoroughness, 305 pieces of literature were surveyed in addition to the author's own experiments. As to forthrightness, here are a few samples of the author's conclusions. "The newer (synthetic) anticholinergic drugs do not perform 'medical

vagotomy'. They have not been proved superior to proper doses of the naturally occurring anticholinergics. There is no single anticholinergic of choice for any gastrointestinal ailment, unless it be atropine or belladonna because of their greatly lower cost."

WALTER CANE

STUDIES ON BILE PIGMENT IN BILE. II. CLINICAL CONSIDERATION ON THE BILIRUBIN CONTENT OF BILE IN PATIENTS WITH VARIOUS BILIARY TRACT DISEASES: Tomonobu Sato. Tohuku J. Exper. Med. 68:293 (25 Oct.), 1958.

The author evaluated 52 patients who underwent laparotomy and classified them into the following four groups:

1. 11 gallstone cases (8 of pigment stone and 3 of cholesterol stone).
2. 5 cases of so-called stoneless cholecystitis.
3. 7 cases of ascariasis of the biliary tract.
4. 26 cases of nonbiliary tract diseases as control.

The gallbladder and common duct bile from these cases was collected by puncture at the time of operation. Of these eight cases (5 of gallstone, 2 of stoneless cholecystitis, and 1 of ascariasis of the biliary tract) were used for evaluation of the bilirubin concentration of the bile.

It was found that the bilirubin content in the bile in pathologic states as compared with those without biliary tract disease was considerably decreased. This was noted particularly in those cases wherein pigment stones were present.

The author also noted that the estimates of the bilirubin content in the gallbladder bile of the Japanese showed a smaller value in comparison with the bile of Caucasians.

MORTON SCHWARTZ

BOOK REVIEWS FOR GASTROENTEROLOGISTS

REGULATION OF CELL METABOLISM: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Cecilia M. O'Connor, B.Sc., Editors for the Ciba Foundation. 387 pages, 109 illustrations. Little, Brown & Co., Boston, Mass., 1959. Price $9.50.

This symposium deals with basic cell research and it may be of great interest to physiologists and biologists who devote their entire time to this theme.

The list of contributors are known for their research and keen observations, but the book is not recommended to the general practitioners of medicine unless they are interested in delving further into the mysteries of the cell.

EISENSTOFFWECHSEL (IRON SYNTHESIS)—BEITRAGE ZUR FORSCHUNG UND KLINIK: with the editorial cooperation of M. Bessis; K. Betke; H. J. Bielig; S. E. Bjorkman; P. Buchmann; J. C. Doreyfus; R. Dubach; C. A. Finch; T. M. Fliedner; A. Gajdos; G. Hemmeler; W. Kriedling; C. B. Laurell; J. H. Lawrence; C. V. Moore; H. G. Parker; M. Pollycove; W. Pribilla; K. R. Reissman; K. H. Schafer; G. Schapira; H. A. Schmidt; H. Schulten; B. Steiner; R. Stodtmeister; E. Undritz; B. Vahlquist; A. Varinotti; J. Walderstrom; F. Wohler. 294 pages, 138 illustrations, many in color. Georg Thieme Verlag, Stuttgart, Germany, 1959. Price $11.40.

A *festschrift* in honor of Professor Dr. Ludwig Heilmeyer on his 60th birthday, this book is a tribute to his many years as a clinician and investigator, especially of the synthesis and absorption of iron by the human body, its disposition in the various organs and its effect on these organs and electrolytes.

It is a very interesting and highly technical treatise in German and English, beautifully printed and illustrated with an extensive literature.

NIERENKRANKHEITEN—PHYSIOLOGIE, PATHOPHYSIOLOGIE, UNTERSUCHUNGSMETHODEN, KLINIK UND THERAPY: Prof. H. Sarre, D. Med., O.O. Professor der Inneren Medizin, Direktor der Medizinischen, Universitats Poliklinik, Freiburg/Br. 2nd Edition. 555 pages, 134 illustrations. Georg Thieme Verlag, Stuttgart, Germany, 1959. Price $14.05.

The second edition of this volume on kidney diseases follows closely the first edition which appeared approximately one year ago. This alone shows that the previous volume was well received by the medical profession, necessitating a second revised edition with numerous added tables and illustrations.

The present text has five divisions of 45 chapters, to which is added the world's literature between 1950-1957 and an extensive cross index.

Extensive tables of normal values and diets add a great deal to this beautifully printed, illustrated and bound text.

It is highly recommended that an English translation be considered. Physicians, however, and others interested in kidney diseases and those who can read German, will find it useful in their practice.

CHOLINESTERASES—A HISTOCHEMICAL CONTRIBUTION TO THE SOLUTION OF SOME FUNCTIONAL PROBLEMS: M. A. Gerebtzoff, Department of Anatomy, Liege University. 195 pages, illustrated. Pergamon Press, Inc., New York, N. Y., 1959. Price $8.50.

A very interesting discussion on the probable hepatic origin of plasmatic cholinesterases is found on page 8. Physicians who are interested and treat liver diseases, will be well repaid for the time they take to read this valuable dissertation.

Extensive references, name and cross index complete the book.

It is highly recommended.

HEALTH PHYSICS INSTRUMENTATION: John S. Handloser, Brookhaven National Laboratory, Upton, N. Y. 182 pages, illustrated. Pergamon Press, Inc., New York, N. Y., 1959. Price $6.50.

Physicists and radiation workers will find useful information in this compact book.

Valuable references follow each chapter and there is an adequate cross index.

ABC FUR ZUCKERKRANKE: Prof. Dr. Ferdinand Bertram, chem. Chefartz der II Medizinischen Klinik des Allgemeinen Krankenhauses Barmbek, Hamburg. Tenth Revised Edition. 88 pages, several illustrations and tables. Georg Thieme Verlag, Stuttgart, Germany, 1959. Price $1.00.

This edition of the ABC of Diabetes is dedicated by the author to Dr. Elliot P. Joslin of Boston on his 90th birthday.

It is a small book, useful to both the doctor and the patient. Besides the use of insulin, Orinase and other oral therapy are discussed.

On page 55, the reader will find the various oral preparations with and without sulfa. It is interesting to note how many of these are used under different names in different localities. Pages 58 and 59 describe the dose and possible complications occurring from administering the medication.

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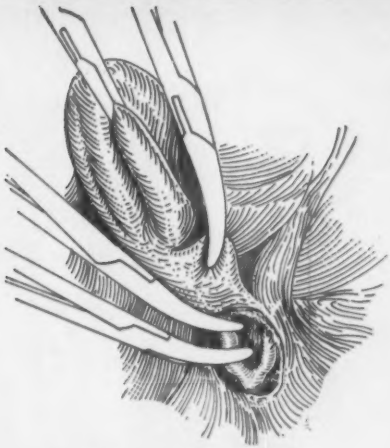

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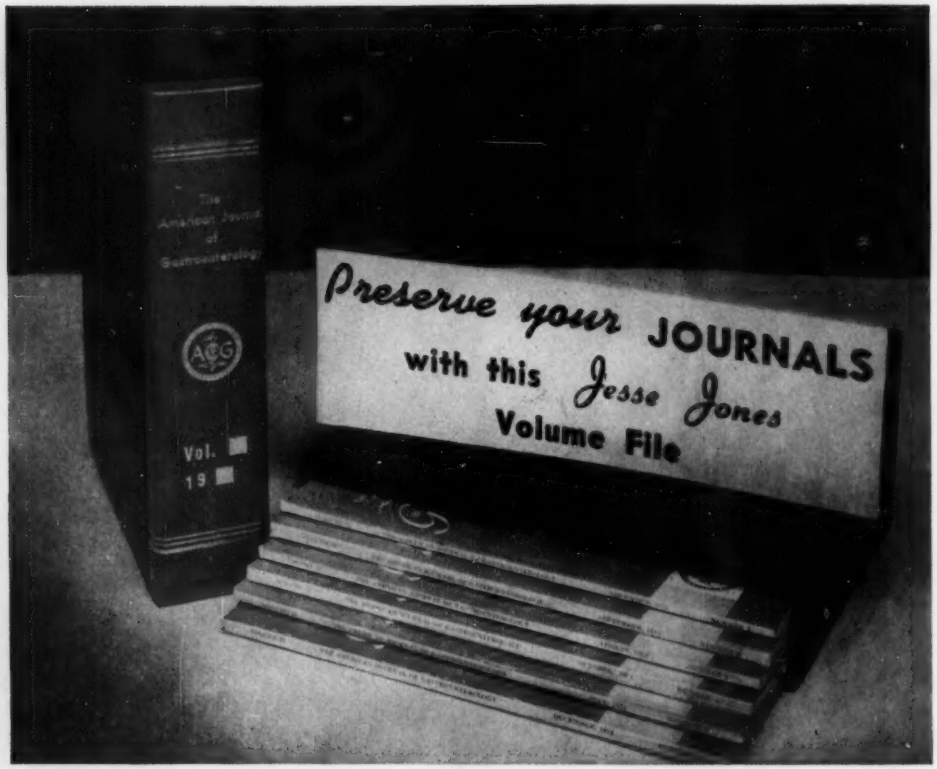
Source: **Farris, J. M., and Smith, G. K.: M. Clin. North America *43*:1133 (July) 1959.**



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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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1. Weiss, J.: Amer. J. Gastroent., July 1960.
2. Breidenbach, L. and Secor, S. M.: Amer. J. Surg., Jan. 1957.

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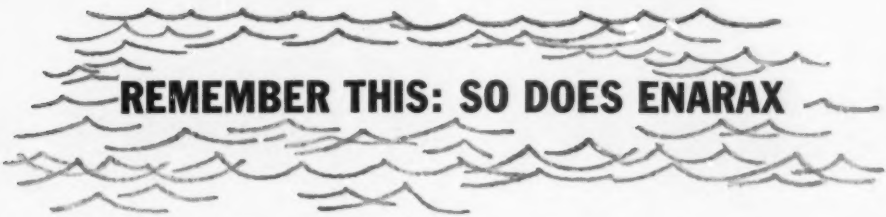

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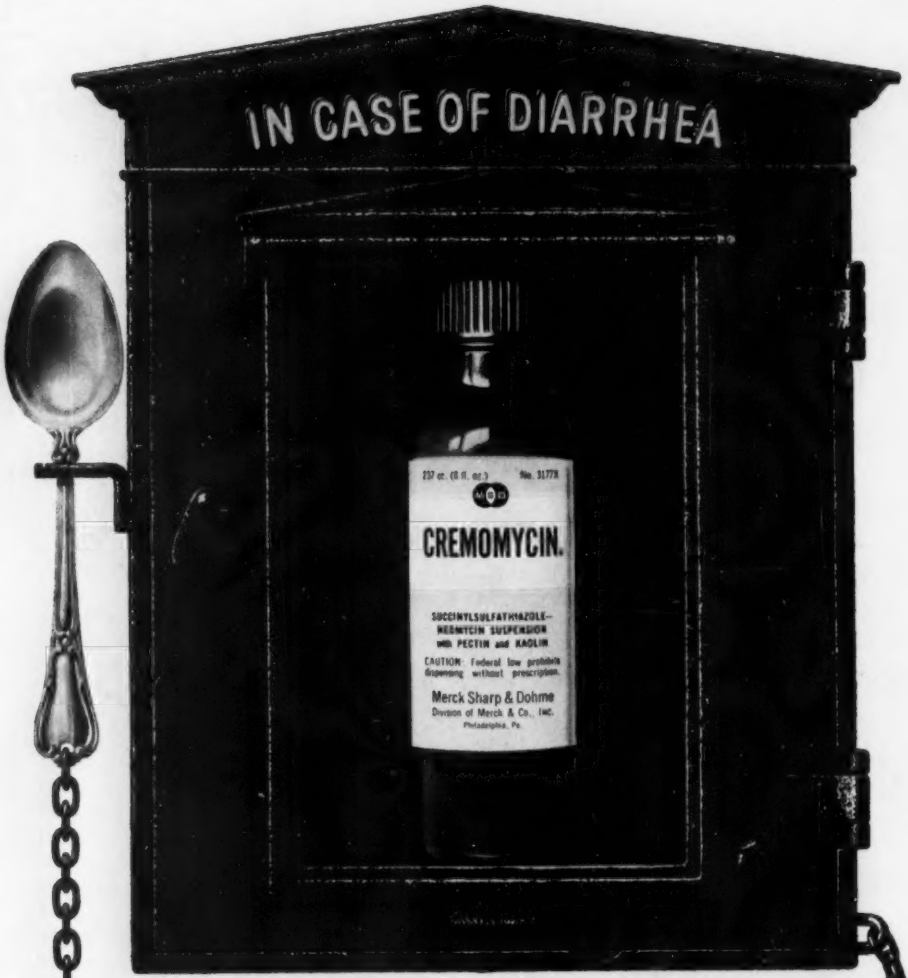

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